Docket No.: 029163.00018-US00
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Valentino J. Stella et al.

U.S. Patent No.: 6,204,257

Issued: March 20, 2001

For: WATER SOLUBLE PRODRUGS OF HINDERED ALCOHOLS

TRANSMITTAL LETTER

Mail Stop: Hatch-Waxman PTE
U.S. Patent and Trademark Office
Office of Patent Legal Administration
Room MDW 7D55
600 Dulany Street (Madison Building)
Alexandria, VA 22313

Dear Madam:

Enclosed are the following items for filing in connection with the above-referenced Patent Application:

1. Fee Transmittal;

2. Request for Extension of Patent Term under 35 U.S.C. § 156 (original plus three copies) together with Exhibits 1-11 (original plus two copies);

3. Check No. 402768 for $1,120.00 to cover the fee for a Request for Extension of Patent Term; and

4. Return receipt postcard.

Our check in the amount of $1,120.00 covering the required fees is enclosed. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by

this firm) to our Deposit Account No. 50-0740, under Docket No. 029163.00018-US00. A duplicate copy of this paper is enclosed.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 50-0740.

Dated: February 6, 2009

Respectfully submitted,

By _____
Natalie M. Derzko
Registration No.: 48,102
COVINGTON & BURLING LLP
1201 Pennsylvania Avenue, N.W.
Washington, DC 20004-2401
(202) 662-6000

Docket No.: 029163.00018-US00
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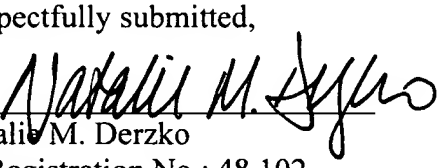
By 

Natalie M. Derzko
Registration No.: 48,102
COVINGTON & BURLING LLP
1201 Pennsylvania Avenue, N.W.
Washington, DC 20004-2401
(202) 662-6000

PTO/SB/17 (10-08)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2009

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 1,120.00

Complete if Known	
Application Number	Patent#: 6,204,257
Filing Date	Issued: March 20, 2001
First Named Inventor	Valentino J. Stella
Examiner Name	N/A
Art Unit	N/A
Attorney Docket No.	029163.00018-US00

METHOD OF PAYMENT (check all that apply)

☒ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☐ Deposit Account Deposit Account Number: 50-0740 Deposit Account Name: Covington & Burling LLP

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☐ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☒ Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17 ☒ Credit any overpayments

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
Application Type	Fee ($)	Small Entity Fee ($)	Fee ($)	Small Entity Fee ($)	Fee ($)	Small Entity Fee ($)	Fees Paid ($)
Utility	330	165	540	270	220	110	
Design	220	110	100	50	140	70	
Plant	220	110	330	165	170	85	
Reissue	330	165	540	270	650	325	
Provisional	220	110	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	52	26
Each independent claim over 3 (including Reissues)	220	110
Multiple dependent claims	390	195

Total Claims _____ - 20 or HP _____ x Fee ($) _____ = Fee Paid ($) _____

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims _____ - 3 or HP = _____ x Fee ($) _____ = Fee Paid ($) _____

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims — Fee ($) _____ Fee Paid ($) _____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $270 ($135 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets _____ - 100 = _____ Extra Sheets _____ /50 = _____ Number of each additional 50 or fraction thereof (round up to a whole number) x Fee ($) _____ = Fee Paid ($) _____

4. OTHER FEE(S) Fees Paid ($)

Non-English Specification, $130 fee (no small entity discount)

Other (e.g., late filing surcharge): 1457 Extension of term of patent 1,120.00

SUBMITTED BY					
Signature	Natalie M. Derzko	Registration No. (Attorney/Agent)	48,102	Telephone	(202) 662-5301
Name (Print/Type)	Natalie M. Derzko			Date	February 6, 2009

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent of:
Stella et al.

Patent No.: 6,204,257

Issued: March 20, 2001

For: Water-Soluble Prodrugs of Hindered Alcohols

Mail Stop: Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA
22313-1450

REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Sir:

Pursuant to 35 U.S.C. §156 and 37 C.F.R. §§1.710-1.791, Applicant, the University of Kansas, the address of which is Center for Drug Delivery Research, 2095 Constant Avenue, Lawrence, Kansas, 66047, represents that it is the owner and assignee of the entire interest in and to Letters Patent of the United States No. 6,204,257 (Exhibit 1, the "'257 patent") granted to Valentino J. Stella, Jan J. Zygmunt, Ingrid Gunda Georg, and Muhammad S. Safadi on the 20th day of March, 2001, for "Water Soluble Prodrugs of Hindered Alcohols," by virtue of an assignment from Valentino J. Stella, Jan J. Zygmunt, Ingrid Gunda Georg, and Muhammad S. Safadi to the University of Kansas, recorded January 14, 1999 at Reel 009699, Frame 0961. (Exhibit 2). The '257 patent matured from United States Patent Application No. 09/131,385, filed August 7, 1998.

The approved product that is relevant to this application is LUSEDRA™ (fospropofol disodium) Injection, 35 mg/ml, for intravenous use, referred to herein as "LUSEDRA" or "Approved Product."

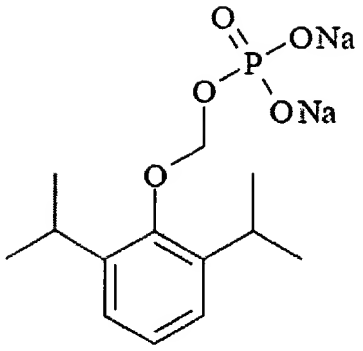
The Marketing Applicant for LUSEDRA is Eisai Medical Research Inc., of 6611 Tributary Street, Baltimore, MD, 21224-6515, a wholly-owned subsidiary of Eisai Co., Ltd., headquartered in Tokyo, Japan. A letter on behalf of the Marketing Applicant authorizing the patent owner to rely upon the activities of the Marketing Applicant, its predecessors, and affiliates is attached hereto as Exhibit 3.

The following information is submitted by Eisai Medical Research, Inc., through its duly authorized attorney, on behalf of Applicant (see Exhibit 4), in accordance with 35 U.S.C. §156(d) and the rules for extension of patent term issued by the USPTO at 37 C.F.R. Subpart F, §§1.710 to 1.791 and follows the numerical format set forth in 37 C.F.R. §1.740.

(1) A COMPLETE IDENTIFICATION OF THE APPROVED PRODUCT AS BY APPROPRIATE CHEMICAL AND GENERIC NAME, PHYSICAL STRUCTURE OR CHARACTERISTICS:

The approved product is LUSEDRA, a formulation with the active ingredient fospropofol disodium at a concentration of 35 mg/ml. LUSEDRA has been approved for intravenous administration as a sedative-hypnotic agent for monitored anesthesia care (MAC) sedation in adult patients undergoing diagnostic or therapeutic procedures (approved label attached as Exhibit 5.)

The chemical name of fospropofol disodium is 2,6-diisopropylphenoxymethyl phosphate, disodium salt, with the chemical structure:



Fospropofol disodium is a water soluble phosphonooxymethyl derivative of the previously-approved drug propofol. Following administration, fospropofol is dephosphorylated by endogenous alkaline phosphatases to release propofol.

(2) A COMPLETE IDENTIFICATION OF THE FEDERAL STATUTE INCLUDING THE APPLICABLE PROVISION OF LAW UNDER WHICH THE REGULATORY REVIEW OCCURRED:

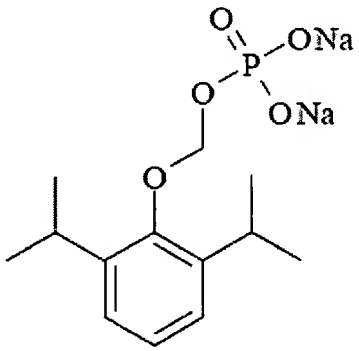
The approved product is a drug product and the submission was approved under Section 505(b) of the Federal Food, Drug, and Cosmetic Act ("FFDCA") (21 U.S.C. § 355(b)).

(3) AN IDENTIFICATION OF THE DATE ON WHICH THE PRODUCT RECEIVED PERMISSION FOR COMMERCIAL MARKETING OR USE UNDER THE PROVISION OF LAW UNDER WHICH THE APPLICABLE REGULATORY REVIEW PERIOD OCCURRED:

The Approved Product received permission for commercial marketing or use by the Food and Drug Administration ("FDA") pursuant to Section 505(b) of the FFDCA in a letter dated December 12, 2008. A copy of the approval letter is attached as Exhibit 6.

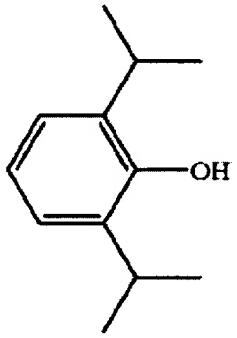
(4) IN THE CASE OF A DRUG PRODUCT, AN IDENTIFICATION OF EACH ACTIVE INGREDIENT IN THE PRODUCT AND AS TO EACH ACTIVE INGREDIENT, A STATEMENT THAT IT HAS NOT BEEN PREVIOUSLY APPROVED FOR COMMERCIAL MARKETING OR USE UNDER THE FFDCA, THE PUBLIC HEALTH SERVICE ACT, OR THE VIRUS-SERUM-TOXIN ACT OR A STATEMENT OF WHEN THE ACTIVE INGREDIENT WAS APPROVED FOR COMMERCIAL MARKETING OR USE (EITHER ALONE OR IN COMBINATION WITH OTHER ACTIVE INGREDIENTS), THE USE FOR WHICH IT WAS APPROVED, AND THE PROVISION OF LAW UNDER WHICH IT WAS APPROVED: (37 C.F.R. § 1.740(a)(4))

LUSEDRA has been approved under Section 505(b) of the FFDCA as a sedative-hypnotic agent for monitored anesthesia care (MAC) sedation in adult patients undergoing diagnostic or therapeutic procedures. The active ingredient in LUSEDRA is fospropofol disodium, with the chemical structure:



LUSEDRA is a novel phosphonooxymethyl derivative of the drug propofol. Following administration, Fospropofol is converted to the drug propofol by alkaline phosphatases. Propofol, the active metabolite of fospropofol, has been previously approved for marketing and use by the U.S. Food and Drug Administration ("FDA"). FDA-approved products

including propofol include Diprivan®, marketed by AstraZeneca Pharmaceuticals LP. Propofol has the structure depicted below:



Fospropofol is not a direct phosphate ester of propofol, but is instead a phosphonooxymethyl derivative.

Neither fospropofol disodium, nor any salt or ester of that active ingredient, have been previously approved for commercial marketing or use under the FFDCA, the Public Health Service Act, or the Virus-Serum-Toxin Act. In addition, no drug product having the same fospropofol active moiety, as defined in 21 C.F.R. § 314.108(a), as LUSEDRA has previously been approved for commercial marketing or use under the FFDCA, the Public Health Service Act, or the Virus-Serum-Toxin Act, and FDA has determined that LUSEDRA is a New Molecular Entity.

(5) A STATEMENT THAT THE APPLICATION IS BEING SUBMITTED WITHIN THE SIXTY DAY PERIOD PERMITTED FOR SUBMISSION PURSUANT TO SECTION 1.720(f) AND AN IDENTIFICATION OF THE DATE OF THE LAST DAY ON WHICH THE APPLICATION COULD BE SUBMITTED:

This Application is timely filed, pursuant to 35 U.S.C. § 156(d)(1), within the permitted sixty-day (60-day) period that began on December 12, 2008 when the product received

permission under 21 U.S.C. § 355(b) and that will expire on February 10, 2009. Applicant understands that, pursuant to 37 C.F.R. § 1.720(f), the USPTO may deem this period to expire one day earlier, on February 9, 2009.

(6) A COMPLETE IDENTIFICATION OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT BY THE NAME OF THE INVENTOR, THE PATENT NUMBER, THE DATE OF ISSUE, AND THE DATE OF EXPIRATION:

UNITED STATES PATENT NO.: 6,204,257

INVENTORS: STELLA, ET AL.

DATE OF ISSUE: MARCH 20, 2001

EXPIRATION DATE: AUGUST 7, 2018

The expiration date of U.S. Patent No. 6,204,257 ("the '257 patent") is August 7, 2018 based on the following: The patent application, U.S. Application No. 09/131,385 ("the '385 application"), was filed on August 7, 1998 and does not claim priority from any other application. Thus, the earliest priority date of the '385 application is August 7, 1998. The '385 application matured into the '257 patent, which issued on March 20, 2001. The '257 patent is entitled to an expiration date that is 20 years from the earliest priority date, which is August 7, 2018.

(7) A COPY OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT, INCLUDING THE ENTIRE SPECIFICATION (INCLUDING CLAIMS) AND DRAWINGS:

A complete copy of U.S. Patent No. 6,204,257 is attached as Exhibit 1.

(8) A COPY OF ANY DISCLAIMER, CERTIFICATE OF CORRECTION, RECEIPT OF MAINTENANCE FEE PAYMENT, OR RE-EXAMINATION CERTIFICATE ISSUED IN THE PATENT:

No disclaimers were filed for U.S. Patent No. 6,204,257.

United States Patent No. 6,204,257 has not been re-examined, and so no re-examination certificate has been issued.

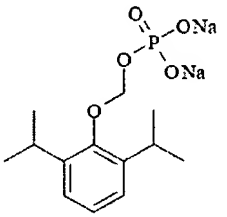
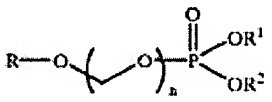
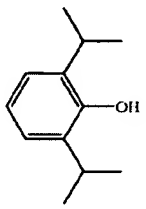
No certificates of correction have been filed for U.S. Patent No. 6,204,257.

The first maintenance fee for U.S. Patent No. 6,204,257 was paid August 17, 2004, and the second maintenance fee was paid September 22, 2008, as shown by the Patent Bibliographic Data Sheet and USPTO Maintenance Fee Statements dated February 5, 2009, all found in Exhibit 7. The next maintenance fee is not yet due. Accordingly, there are no unpaid maintenance fees for this patent.

(9) A STATEMENT THAT THE PATENT CLAIMS THE APPROVED PRODUCT, OR A METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT, AND A SHOWING WHICH LISTS EACH APPLICABLE PATENT CLAIM AND DEMONSTRATES THE MANNER IN WHICH AT LEAST ONE SUCH PATENT CLAIM READS ON THE APPROVED PRODUCT OR A METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT:

U.S. Patent No. 6,204,257 claims the Approved Product and methods of using the Approved Product. Specifically, at least claims 1-5, 9, 11, 13-17 and 21-24 read on the Approved Product and the approved methods of use. Pursuant to 37 C.F.R. § 1.740(a)(9), a

showing which demonstrates the manner in which one product claim and one method of use claim read on the approved product and method of using the approved product is set forth herein below.

CLAIM	ELEMENTS
1. A compound according to formula **I**:  wherein, R–O– is a residue of a phenol containing pharmaceutical compound R^1 Is hydrogen or an alkali metal ion or a protonated amine or a protonated amino acid, R^2 is hydrogen or an alkali metal ion or a protonated amine or a protonated amino acid, n is an integer of 1 or 2; and pharmaceutically acceptable salts thereof.	The active ingredient in LUSEDRA is Fospropofol disodium:  Fospropofol disodium is the compound of formula I,  wherein: R–O– is a residue of propofol (below), which is a phenol containing pharmaceutical compound:  R^1 is Na, an alkali metal ion, R^2 is Na, an alkali metal ion, and n=1.
11. A method of treatment which produces an anesthetic effect comprising administering to a patient in need thereof an effective amount of a composition according to claim **1**.	LUSEDRA is approved as an intravenous sedative-hypnotic agent indicated for monitored anesthesia care (MAC) sedation in adult patients undergoing diagnostic or therapeutic procedures, and is a composition according to claim 1.

(10) A STATEMENT BEGINNING ON A NEW PAGE OF THE RELEVANT DATES AND INFORMATION PURSUANT TO 35 U.S.C. §156(g) IN ORDER TO ENABLE THE SECRETARY OF HEALTH AND HUMAN SERVICES OR THE SECRETARY OF AGRICULTURE, AS APPROPRIATE, TO DETERMINE THE APPLICABLE REGULATORY REVIEW PERIOD AS FOLLOWS:

(i) FOR A PATENT CLAIMING A HUMAN DRUG, ANTIBIOTIC, OR HUMAN BIOLOGICAL PRODUCT, THE EFFECTIVE DATE OF THE INVESTIGATIONAL NEW DRUG APPLICATION (IND) AND THE IND NUMBER; THE DATE ON WHICH A NEW DRUG APPLICATION (NDA) OR A PRODUCT LICENSE APPLICATION (PLA) WAS INITIALLY SUBMITTED AND THE NDA OR PLA NUMBER; AND THE DATE ON WHICH THE NDA WAS APPROVED OR THE PRODUCT LICENSE ISSUED:

An original investigational new drug application ("IND") was filed on June 29, 2001, and assigned IND No. 62,860. A copy of the letter acknowledging receipt of the IND is attached as Exhibit 8.

Following submission, the IND was placed on inactive status by FDA in response to a request by the applicant filed July 27, 2001. On April 12, 2002, a letter was filed requesting reactivation of IND No. 62,860. In a letter dated April 19, 2002, FDA acknowledged receipt of the request for reactivation on April 15, 2002. (Exhibit 9). Accordingly, IND No. 62,860 became effective 30 days from April 15, 2002, which is May 15, 2002.

A new drug application ("NDA") was submitted on September 26, 2007 and acknowledged as received on September 27, 2007, in a letter from FDA dated October 15, 2007. (Exhibit 10). The NDA number assigned to the application for fospropofol disodium (under the

proposed name AQUAVAN®) was assigned NDA number 22-244. Accordingly, the NDA was initially submitted on September 26, 2007. The NDA was approved on December 12, 2008. (Exhibit 6).

(11) A BRIEF DESCRIPTION BEGINNING ON A NEW PAGE OF THE SIGNIFICANT ACTIVITIES UNDERTAKEN BY OWNER, THE MARKETING APPLICANT, DURING THE APPLICABLE REGULATORY REVIEW PERIOD WITH RESPECT TO THE APPROVED PRODUCT AND THE SIGNIFICANT DATES APPLICABLE TO SUCH ACTIVITIES:

In accordance with 37 C.F.R. § 1.740(a)(11), a list of significant activities, undertaken by the Marketing Applicant, its predecessor, and affiliates, in IND No. 62,860 and NDA No. 22-244 during the applicable regulatory review period with respect of the approved product is provided at Exhibit 11.

(12) A STATEMENT BEGINNING ON A NEW PAGE THAT IN THE OPINION OF THE APPLICANT THE PATENT IS ELIGIBLE FOR THE EXTENSION AND A STATEMENT AS TO THE LENGTH OF EXTENSION CLAIMED, INCLUDING HOW THE LENGTH OF EXTENSION WAS DETERMINED:

(a) Statement of the eligibility of the patent for extension under 35 U.S.C. §156(a):

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted; (2) the term of the patent has never been extended under 35 U.S.C. §156(e)(1); (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. §156(d); (4) the product has been subject to a regulatory review period before its commercial marketing or use; and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product using the provision of law under which such regulatory review period occurred.

As described below by corresponding number, each of these elements is satisfied here:

(1) Pursuant to 35 U.S.C. §154, the term of United States Patent No. 6,204,257 is currently set to expire on August 7, 2018. This application is, therefore, being submitted prior to the expiration of the term of United States Patent No 6,204,257.

(2) The term of this patent has never been extended under 35 U.S.C. §156(e)(1).

(3) This application is being submitted by Eisai Medical Research, Inc., as agent for Applicant, the University of Kansas, the owners of record of United States Patent No. 6,204,257. (See Exhibit 4). The University of Kansas is the owner of record by virtue of duly recorded assignments discussed above. This application is submitted in accordance with 35 U.S.C. §156(d) in that it is submitted within the sixty-day period beginning on December 12, 2008, the date the product received permission for marketing under Section 505 of the FFDCA [21 U.S.C. §355], and ending on February 10, 2009. Moreover, this application contains the information required under 35 U.S.C. §156(d).

(4) As evidenced by the December 12, 2008 letter from the FDA to Eisai Medical Research Inc., submitted as Exhibit 4, the product was subject to a regulatory review period under Section 505(b) of the FFDCA before its commercial marketing or use.

(5) The permission for the commercial marketing of the LUSEDRA™ (fospropofol disodium) product is the first permitted commercial marketing and use under Section 505 of the FFDCA [21 U.S.C. §355] of the product, as defined in 35 U.S.C. § 156(f). (See Section 4, above.)

(b) Statement as to length of extension claimed.

The term of U.S. Patent No. 6,204,257, now expiring August 7, 2018, should be extended for 1,424 days, or to July 1, 2022, in accordance with 35 U.S.C. §156.

As set forth in 35 U.S.C. §156(g)(1), the regulatory review period equals the length of time between the effective date of IND No. 62,860 of May 15, 2002 and the submission of the NDA 22-244 on September 26, 2007 (i.e., the "testing phase"), a period of 1,960 days, plus the length of time between the submission of the NDA 22-244 on September 26, 2007 to

NDA approval on December 12, 2008 (i.e., the "approval phase"), a period of 444 days. These two periods added together equal 2,404 days.

Pursuant to 37 C.F.R. § 1.775(d), the term of the patent as extended is determined by subtracting from the 2,404 day regulatory review period the following:

(i) 0 days, which is the number of days in the IND and NDA periods on or before the issuance of U.S. Patent No. 6,204,257 on March 20, 2001; and

(ii) 980 days, which is one-half the number of days remaining in the IND period after the subtraction of 0 days above (wherein half days are ignored for purposes of this subtraction, as provided by 37 C.F.R. § 1.775(d)(1)(iii)).

From the foregoing calculation, an extension of 1,424 days results, i.e., the remaining period under 35 U.S.C. 156(g)(1)(B)(i) (980 days) plus the remaining period under 35 U.S.C. §156(g)(1)(B)(ii) (444 days). This length of an extension would provide a new expiration date for U.S. Patent No. 6,204,257 of July 1, 2022. However, this extension period is subject to two further potential limitations under 35 U.S.C. §156.

First, under 35 U.S.C. §156(g)(6)(A), a maximum extension of five years is permitted. In this case, since the current expiry date of U.S. Patent No. 6,204,257 is August 7, 2018, no patent term extension could extend the term of the patent beyond August 7, 2023. Consequently, this provision does not operate to limit the possible extension available to U.S. Patent 6,204,257.

Second, under 35 U.S.C. §156(c)(3), if the calculated extension period would lead to a patent term that would result in a patent term exceeding 14 years after the date of approval, that is, a patent term expiring after December 12, 2022, the period of extension would be limited

so that this period does not exceed 14 years. In this case, this provision also does not operate to limit the possible extension available to U.S. Patent 6,204,257.

Accordingly, United States Patent No. 6,204,257 is eligible for a patent term extension for 1,424 days.

(13) A STATEMENT THAT APPLICANT ACKNOWLEDGES A DUTY TO DISCLOSE TO THE COMMISSIONER OF PATENTS AND TRADEMARKS AND THE SECRETARY OF HEALTH AND HUMAN SERVICES ANY INFORMATION WHICH IS MATERIAL TO THE DETERMINATION OF ENTITLEMENT TO THE EXTENSION SOUGHT (SEE 37 C.F.R. §1.765).

The University of Kansas acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

(14) THE PRESCRIBED FEE FOR RECEIVING AND ACTING UPON THE APPLICATION FOR EXTENSION (SEE 37 C.F.R. §1.20(j)):

Accompanying this Request is Check No. 402768 for $1120.00 to cover the fee for a request for extension of patent term. The Director is hereby authorized to charge our Deposit Account No. 50-0740, under Docket No. 029163.00018-US00, for any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm), to prevent this application from being inadvertently abandoned. A duplicate of this Request (without Exhibits 1-11) is attached.

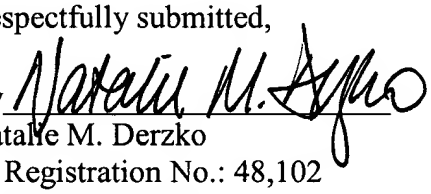
(15) THE NAME, ADDRESS, AND TELEPHONE NUMBER OF THE PERSON TO WHOM INQUIRIES AND CORRESPONDENCE RELATING TO THE APPLICATION FOR PATENT TERM EXTENSION ARE TO BE DIRECTED:

Christopher N. Sipes
COVINGTON & BURLING LLP
1201 Pennsylvania Avenue, N.W.
Washington, DC 20004-2401
Telephone No.: (202) 662-6000
Facsimilie No.: (202) 662-6291

Pursuant to 37 C.F.R. §1.740(b), this Request for Extension of Patent Term Under 35 U.S.C. §156, including Exhibits 1-11, is accompanied by two additional copies, for a total submission of three copies.

Dated: February 6, 2009

Respectfully submitted,

By 

Natalie M. Derzko
Registration No.: 48,102
Christopher N. Sipes
Registration No.: 39,837
COVINGTON & BURLING LLP
1201 Pennsylvania Avenue, N.W.
Washington, DC 20004-2401
(202) 662-6000

Docket No. 029163.00018-US00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent of:
Stella et al.

Patent No.: 6,204,257

Issued: March 20, 2001

For: Water-Soluble Prodrugs of Hindered Alcohols

Mail Stop: Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA
22313-1450

REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Sir:

Pursuant to 35 U.S.C. §156 and 37 C.F.R. §§1.710-1.791, Applicant, the University of Kansas, the address of which is Center for Drug Delivery Research, 2095 Constant Avenue, Lawrence, Kansas, 66047, represents that it is the owner and assignee of the entire interest in and to Letters Patent of the United States No. 6,204,257 (Exhibit 1, the "'257 patent") granted to Valentino J. Stella, Jan J. Zygmunt, Ingrid Gunda Georg, and Muhammad S. Safadi on the 20th day of March, 2001, for "Water Soluble Prodrugs of Hindered Alcohols," by virtue of an assignment from Valentino J. Stella, Jan J. Zygmunt, Ingrid Gunda Georg, and Muhammad S. Safadi to the University of Kansas, recorded January 14, 1999 at Reel 009699, Frame 0961. (Exhibit 2). The '257 patent matured from United States Patent Application No. 09/131,385, filed August 7, 1998.

The approved product that is relevant to this application is LUSEDRA™ (fospropofol disodium) Injection, 35 mg/ml, for intravenous use, referred to herein as "LUSEDRA" or "Approved Product."

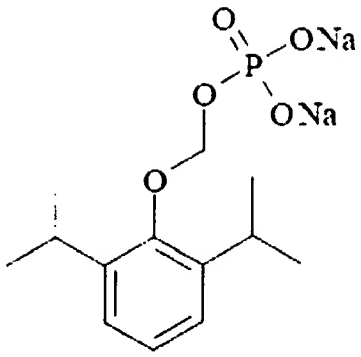
The Marketing Applicant for LUSEDRA is Eisai Medical Research Inc., of 6611 Tributary Street, Baltimore, MD, 21224-6515, a wholly-owned subsidiary of Eisai Co., Ltd., headquartered in Tokyo, Japan. A letter on behalf of the Marketing Applicant authorizing the patent owner to rely upon the activities of the Marketing Applicant, its predecessors, and affiliates is attached hereto as Exhibit 3.

The following information is submitted by Eisai Medical Research, Inc., through its duly authorized attorney, on behalf of Applicant (see Exhibit 4), in accordance with 35 U.S.C. §156(d) and the rules for extension of patent term issued by the USPTO at 37 C.F.R. Subpart F, §§1.710 to 1.791 and follows the numerical format set forth in 37 C.F.R. §1.740.

(1) A COMPLETE IDENTIFICATION OF THE APPROVED PRODUCT AS BY APPROPRIATE CHEMICAL AND GENERIC NAME, PHYSICAL STRUCTURE OR CHARACTERISTICS:

The approved product is LUSEDRA, a formulation with the active ingredient fospropofol disodium at a concentration of 35 mg/ml. LUSEDRA has been approved for intravenous administration as a sedative-hypnotic agent for monitored anesthesia care (MAC) sedation in adult patients undergoing diagnostic or therapeutic procedures (approved label attached as Exhibit 5.)

The chemical name of fospropofol disodium is 2,6-diisopropylphenoxymethyl phosphate, disodium salt, with the chemical structure:



Fospropofol disodium is a water soluble phosphonooxymethyl derivative of the previously-approved drug propofol. Following administration, fospropofol is dephosphorylated by endogenous alkaline phosphatases to release propofol.

(2) A COMPLETE IDENTIFICATION OF THE FEDERAL STATUTE INCLUDING THE APPLICABLE PROVISION OF LAW UNDER WHICH THE REGULATORY REVIEW OCCURRED:

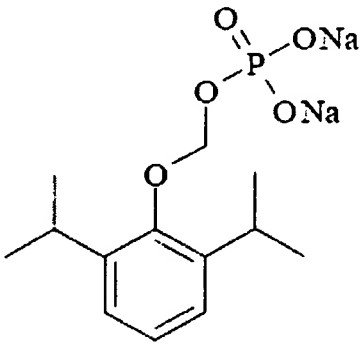
The approved product is a drug product and the submission was approved under Section 505(b) of the Federal Food, Drug, and Cosmetic Act ("FFDCA") (21 U.S.C. § 355(b)).

(3) AN IDENTIFICATION OF THE DATE ON WHICH THE PRODUCT RECEIVED PERMISSION FOR COMMERCIAL MARKETING OR USE UNDER THE PROVISION OF LAW UNDER WHICH THE APPLICABLE REGULATORY REVIEW PERIOD OCCURRED:

The Approved Product received permission for commercial marketing or use by the Food and Drug Administration ("FDA") pursuant to Section 505(b) of the FFDCA in a letter dated December 12, 2008. A copy of the approval letter is attached as Exhibit 6.

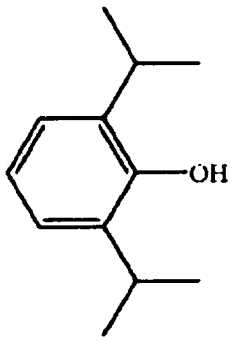
(4) IN THE CASE OF A DRUG PRODUCT, AN IDENTIFICATION OF EACH ACTIVE INGREDIENT IN THE PRODUCT AND AS TO EACH ACTIVE INGREDIENT, A STATEMENT THAT IT HAS NOT BEEN PREVIOUSLY APPROVED FOR COMMERCIAL MARKETING OR USE UNDER THE FFDCA, THE PUBLIC HEALTH SERVICE ACT, OR THE VIRUS-SERUM-TOXIN ACT OR A STATEMENT OF WHEN THE ACTIVE INGREDIENT WAS APPROVED FOR COMMERCIAL MARKETING OR USE (EITHER ALONE OR IN COMBINATION WITH OTHER ACTIVE INGREDIENTS), THE USE FOR WHICH IT WAS APPROVED, AND THE PROVISION OF LAW UNDER WHICH IT WAS APPROVED: (37 C.F.R. § 1.740(a)(4))

LUSEDRA has been approved under Section 505(b) of the FFDCA as a sedative-hypnotic agent for monitored anesthesia care (MAC) sedation in adult patients undergoing diagnostic or therapeutic procedures. The active ingredient in LUSEDRA is fospropofol disodium, with the chemical structure:



LUSEDRA is a novel phosphonooxymethyl derivative of the drug propofol. Following administration, Fospropofol is converted to the drug propofol by alkaline phosphatases. Propofol, the active metabolite of fospropofol, has been previously approved for marketing and use by the U.S. Food and Drug Administration ("FDA"). FDA-approved products

including propofol include Diprivan®, marketed by AstraZeneca Pharmaceuticals LP. Propofol has the structure depicted below:



Fospropofol is not a direct phosphate ester of propofol, but is instead a phosphonooxymethyl derivative.

Neither fospropofol disodium, nor any salt or ester of that active ingredient, have been previously approved for commercial marketing or use under the FFDCA, the Public Health Service Act, or the Virus-Serum-Toxin Act. In addition, no drug product having the same fospropofol active moiety, as defined in 21 C.F.R. § 314.108(a), as LUSEDRA has previously been approved for commercial marketing or use under the FFDCA, the Public Health Service Act, or the Virus-Serum-Toxin Act, and FDA has determined that LUSEDRA is a New Molecular Entity.

(5) A STATEMENT THAT THE APPLICATION IS BEING SUBMITTED WITHIN THE SIXTY DAY PERIOD PERMITTED FOR SUBMISSION PURSUANT TO SECTION 1.720(f) AND AN IDENTIFICATION OF THE DATE OF THE LAST DAY ON WHICH THE APPLICATION COULD BE SUBMITTED:

This Application is timely filed, pursuant to 35 U.S.C. § 156(d)(1), within the permitted sixty-day (60-day) period that began on December 12, 2008 when the product received

permission under 21 U.S.C. § 355(b) and that will expire on February 10, 2009. Applicant understands that, pursuant to 37 C.F.R. § 1.720(f), the USPTO may deem this period to expire one day earlier, on February 9, 2009.

(6) A COMPLETE IDENTIFICATION OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT BY THE NAME OF THE INVENTOR, THE PATENT NUMBER, THE DATE OF ISSUE, AND THE DATE OF EXPIRATION:

UNITED STATES PATENT NO.: 6,204,257

INVENTORS: STELLA, ET AL.

DATE OF ISSUE: MARCH 20, 2001

EXPIRATION DATE: AUGUST 7, 2018

The expiration date of U.S. Patent No. 6,204,257 ("the '257 patent") is August 7, 2018 based on the following: The patent application, U.S. Application No. 09/131,385 ("the '385 application"), was filed on August 7, 1998 and does not claim priority from any other application. Thus, the earliest priority date of the '385 application is August 7, 1998. The '385 application matured into the '257 patent, which issued on March 20, 2001. The '257 patent is entitled to an expiration date that is 20 years from the earliest priority date, which is August 7, 2018.

(7) A COPY OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT, INCLUDING THE ENTIRE SPECIFICATION (INCLUDING CLAIMS) AND DRAWINGS:

A complete copy of U.S. Patent No. 6,204,257 is attached as Exhibit 1.

(8) A COPY OF ANY DISCLAIMER, CERTIFICATE OF CORRECTION, RECEIPT OF MAINTENANCE FEE PAYMENT, OR RE-EXAMINATION CERTIFICATE ISSUED IN THE PATENT:

No disclaimers were filed for U.S. Patent No. 6,204,257.

United States Patent No. 6,204,257 has not been re-examined, and so no re-examination certificate has been issued.

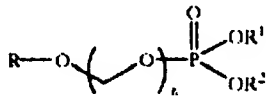
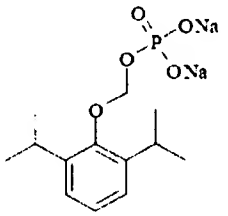
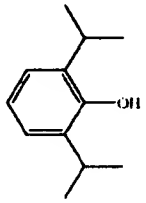
No certificates of correction have been filed for U.S. Patent No. 6,204,257.

The first maintenance fee for U.S. Patent No. 6,204,257 was paid August 17, 2004, and the second maintenance fee was paid September 22, 2008, as shown by the Patent Bibliographic Data Sheet and USPTO Maintenance Fee Statements dated February 5, 2009, all found in Exhibit 7. The next maintenance fee is not yet due. Accordingly, there are no unpaid maintenance fees for this patent.

(9) A STATEMENT THAT THE PATENT CLAIMS THE APPROVED PRODUCT, OR A METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT, AND A SHOWING WHICH LISTS EACH APPLICABLE PATENT CLAIM AND DEMONSTRATES THE MANNER IN WHICH AT LEAST ONE SUCH PATENT CLAIM READS ON THE APPROVED PRODUCT OR A METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT:

U.S. Patent No. 6,204,257 claims the Approved Product and methods of using the Approved Product. Specifically, at least claims 1-5, 9, 11, 13-17 and 21-24 read on the Approved Product and the approved methods of use. Pursuant to 37 C.F.R. § 1.740(a)(9), a

showing which demonstrates the manner in which one product claim and one method of use claim read on the approved product and method of using the approved product is set forth herein below.

CLAIM	ELEMENTS
1. A compound according to formula **I**:  wherein, R–O– is a residue of a phenol containing pharmaceutical compound R^1 Is hydrogen or an alkali metal ion or a protonated amine or a protonated amino acid, R^2 is hydrogen or an alkali metal ion or a protonated amine or a protonated amino acid, n is an integer of 1 or 2; and pharmaceutically acceptable salts thereof.	The active ingredient in LUSEDRA is Fospropofol disodium:  Fospropofol disodium is the compound of formula I,  wherein: R–O– is a residue of propofol (below), which is a phenol containing pharmaceutical compound:  R^1 is Na, an alkali metal ion, R^2 is Na, an alkali metal ion, and n=1.
11. A method of treatment which produces an anesthetic effect comprising administering to a patient in need thereof an effective amount of a composition according to claim **1**.	LUSEDRA is approved as an intravenous sedative-hypnotic agent indicated for monitored anesthesia care (MAC) sedation in adult patients undergoing diagnostic or therapeutic procedures, and is a composition according to claim 1.

(10) A STATEMENT BEGINNING ON A NEW PAGE OF THE RELEVANT DATES AND INFORMATION PURSUANT TO 35 U.S.C. §156(g) IN ORDER TO ENABLE THE SECRETARY OF HEALTH AND HUMAN SERVICES OR THE SECRETARY OF AGRICULTURE, AS APPROPRIATE, TO DETERMINE THE APPLICABLE REGULATORY REVIEW PERIOD AS FOLLOWS:

(i) FOR A PATENT CLAIMING A HUMAN DRUG, ANTIBIOTIC, OR HUMAN BIOLOGICAL PRODUCT, THE EFFECTIVE DATE OF THE INVESTIGATIONAL NEW DRUG APPLICATION (IND) AND THE IND NUMBER; THE DATE ON WHICH A NEW DRUG APPLICATION (NDA) OR A PRODUCT LICENSE APPLICATION (PLA) WAS INITIALLY SUBMITTED AND THE NDA OR PLA NUMBER; AND THE DATE ON WHICH THE NDA WAS APPROVED OR THE PRODUCT LICENSE ISSUED:

An original investigational new drug application ("IND") was filed on June 29, 2001, and assigned IND No. 62,860. A copy of the letter acknowledging receipt of the IND is attached as Exhibit 8.

Following submission, the IND was placed on inactive status by FDA in response to a request by the applicant filed July 27, 2001. On April 12, 2002, a letter was filed requesting reactivation of IND No. 62,860. In a letter dated April 19, 2002, FDA acknowledged receipt of the request for reactivation on April 15, 2002. (Exhibit 9). Accordingly, IND No. 62,860 became effective 30 days from April 15, 2002, which is May 15, 2002.

A new drug application ("NDA") was submitted on September 26, 2007 and acknowledged as received on September 27, 2007, in a letter from FDA dated October 15, 2007. (Exhibit 10). The NDA number assigned to the application for fospropofol disodium (under the

proposed name AQUAVAN®) was assigned NDA number 22-244. Accordingly, the NDA was initially submitted on September 26, 2007. The NDA was approved on December 12, 2008. (Exhibit 6).

(11) A BRIEF DESCRIPTION BEGINNING ON A NEW PAGE OF THE SIGNIFICANT ACTIVITIES UNDERTAKEN BY OWNER, THE MARKETING APPLICANT, DURING THE APPLICABLE REGULATORY REVIEW PERIOD WITH RESPECT TO THE APPROVED PRODUCT AND THE SIGNIFICANT DATES APPLICABLE TO SUCH ACTIVITIES:

In accordance with 37 C.F.R. § 1.740(a)(11), a list of significant activities, undertaken by the Marketing Applicant, its predecessor, and affiliates, in IND No. 62,860 and NDA No. 22-244 during the applicable regulatory review period with respect of the approved product is provided at Exhibit 11.

(12) A STATEMENT BEGINNING ON A NEW PAGE THAT IN THE OPINION OF THE APPLICANT THE PATENT IS ELIGIBLE FOR THE EXTENSION AND A STATEMENT AS TO THE LENGTH OF EXTENSION CLAIMED, INCLUDING HOW THE LENGTH OF EXTENSION WAS DETERMINED:

(a) Statement of the eligibility of the patent for extension under 35 U.S.C. §156(a):

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted; (2) the term of the patent has never been extended under 35 U.S.C. §156(e)(1); (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. §156(d); (4) the product has been subject to a regulatory review period before its commercial marketing or use; and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product using the provision of law under which such regulatory review period occurred.

As described below by corresponding number, each of these elements is satisfied here:

(1) Pursuant to 35 U.S.C. §154, the term of United States Patent No. 6,204,257 is currently set to expire on August 7, 2018. This application is, therefore, being submitted prior to the expiration of the term of United States Patent No 6,204,257.

(2) The term of this patent has never been extended under 35 U.S.C. §156(e)(1).

(3) This application is being submitted by Eisai Medical Research, Inc., as agent for Applicant, the University of Kansas, the owners of record of United States Patent No. 6,204,257. (See Exhibit 4). The University of Kansas is the owner of record by virtue of duly recorded assignments discussed above. This application is submitted in accordance with 35 U.S.C. §156(d) in that it is submitted within the sixty-day period beginning on December 12, 2008, the date the product received permission for marketing under Section 505 of the FFDCA [21 U.S.C. §355], and ending on February 10, 2009. Moreover, this application contains the information required under 35 U.S.C. §156(d).

(4) As evidenced by the December 12, 2008 letter from the FDA to Eisai Medical Research Inc., submitted as Exhibit 4, the product was subject to a regulatory review period under Section 505(b) of the FFDCA before its commercial marketing or use.

(5) The permission for the commercial marketing of the LUSEDRA™ (fospropofol disodium) product is the first permitted commercial marketing and use under Section 505 of the FFDCA [21 U.S.C. §355] of the product, as defined in 35 U.S.C. § 156(f). (See Section 4, above.)

(b) Statement as to length of extension claimed.

The term of U.S. Patent No. 6,204,257, now expiring August 7, 2018, should be extended for 1,424 days, or to July 1, 2022, in accordance with 35 U.S.C. §156.

As set forth in 35 U.S.C. §156(g)(1), the regulatory review period equals the length of time between the effective date of IND No. 62,860 of May 15, 2002 and the submission of the NDA 22-244 on September 26, 2007 (i.e., the "testing phase"), a period of 1,960 days, plus the length of time between the submission of the NDA 22-244 on September 26, 2007 to

NDA approval on December 12, 2008 (i.e., the "approval phase"), a period of 444 days. These two periods added together equal 2,404 days.

Pursuant to 37 C.F.R. § 1.775(d), the term of the patent as extended is determined by subtracting from the 2,404 day regulatory review period the following:

(i) 0 days, which is the number of days in the IND and NDA periods on or before the issuance of U.S. Patent No. 6,204,257 on March 20, 2001; and

(ii) 980 days, which is one-half the number of days remaining in the IND period after the subtraction of 0 days above (wherein half days are ignored for purposes of this subtraction, as provided by 37 C.F.R. § 1.775(d)(1)(iii)).

From the foregoing calculation, an extension of 1,424 days results, i.e., the remaining period under 35 U.S.C. 156(g)(1)(B)(i) (980 days) plus the remaining period under 35 U.S.C. §156(g)(1)(B)(ii) (444 days). This length of an extension would provide a new expiration date for U.S. Patent No. 6,204,257 of July 1, 2022. However, this extension period is subject to two further potential limitations under 35 U.S.C. §156.

First, under 35 U.S.C. §156(g)(6)(A), a maximum extension of five years is permitted. In this case, since the current expiry date of U.S. Patent No. 6,204,257 is August 7, 2018, no patent term extension could extend the term of the patent beyond August 7, 2023. Consequently, this provision does not operate to limit the possible extension available to U.S. Patent 6,204,257.

Second, under 35 U.S.C. §156(c)(3), if the calculated extension period would lead to a patent term that would result in a patent term exceeding 14 years after the date of approval, that is, a patent term expiring after December 12, 2022, the period of extension would be limited

so that this period does not exceed 14 years. In this case, this provision also does not operate to limit the possible extension available to U.S. Patent 6,204,257.

Accordingly, United States Patent No. 6,204,257 is eligible for a patent term extension for 1,424 days.

(13) A STATEMENT THAT APPLICANT ACKNOWLEDGES A DUTY TO DISCLOSE TO THE COMMISSIONER OF PATENTS AND TRADEMARKS AND THE SECRETARY OF HEALTH AND HUMAN SERVICES ANY INFORMATION WHICH IS MATERIAL TO THE DETERMINATION OF ENTITLEMENT TO THE EXTENSION SOUGHT (SEE 37 C.F.R. §1.765).

The University of Kansas acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

(14) THE PRESCRIBED FEE FOR RECEIVING AND ACTING UPON THE APPLICATION FOR EXTENSION (SEE 37 C.F.R. §1.20(j)):

Accompanying this Request is Check No. 402768 for $1120.00 to cover the fee for a request for extension of patent term. The Director is hereby authorized to charge our Deposit Account No. 50-0740, under Docket No. 029163.00018-US00, for any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm), to prevent this application from being inadvertently abandoned. A duplicate of this Request (without Exhibits 1-11) is attached.

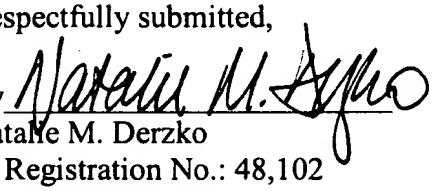
(15) THE NAME, ADDRESS, AND TELEPHONE NUMBER OF THE PERSON TO WHOM INQUIRIES AND CORRESPONDENCE RELATING TO THE APPLICATION FOR PATENT TERM EXTENSION ARE TO BE DIRECTED:

Christopher N. Sipes
COVINGTON & BURLING LLP
1201 Pennsylvania Avenue, N.W.
Washington, DC 20004-2401
Telephone No.: (202) 662-6000
Facsimilie No.: (202) 662-6291

Pursuant to 37 C.F.R. §1.740(b), this Request for Extension of Patent Term Under 35 U.S.C. §156, including Exhibits 1-11, is accompanied by two additional copies, for a total submission of three copies.

Dated: February 6, 2009

Respectfully submitted,

By 

Natalie M. Derzko
Registration No.: 48,102
Christopher N. Sipes
Registration No.: 39,837
COVINGTON & BURLING LLP
1201 Pennsylvania Avenue, N.W.
Washington, DC 20004-2401
(202) 662-6000

US006204257B1

Exhibit 1

(12) **United States Patent**
Stella et al.

(10) **Patent No.: US 6,204,257 B1**
(45) **Date of Patent: Mar. 20, 2001**

(54) **WATER SOLUBLE PRODRUGS OF HINDERED ALCOHOLS**

(75) Inventors: **Valentino J. Stella**, Lawrence, KS (US); **Jan J. Zygmunt**, Longmont, CO (US); **Ingrid Gunda Georg**, Lawrence, KS (US); **Muhammad S. Safadi**, Nazareth (IL)

(73) Assignee: **Universtiy of Kansas**, Lawrence, KS (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/131,385**

(22) Filed: **Aug. 7, 1998**

(51) **Int. Cl.**[7] **A61K 31/661**; C07F 9/06

(52) **U.S. Cl.** **514/130**; 558/187; 558/177; 549/298; 549/408; 514/458; 514/731; 514/768

(58) **Field of Search** 558/187, 177; 568/716; 514/130, 731, 458, 768; 549/298, 408

(56) **References Cited**

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747385A1	12/1996	(EP) .

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(74) *Attorney, Agent, or Firm*—Leonard R. Svensson; Birch, Stewart, Kolasch & Birch, LLP

(57) **ABSTRACT**

The present invention is directed to novel water-soluble prodrugs of aliphatic or aromatic hindered hydroxyl group containing pharmaceuticals.

28 Claims, 4 Drawing Sheets

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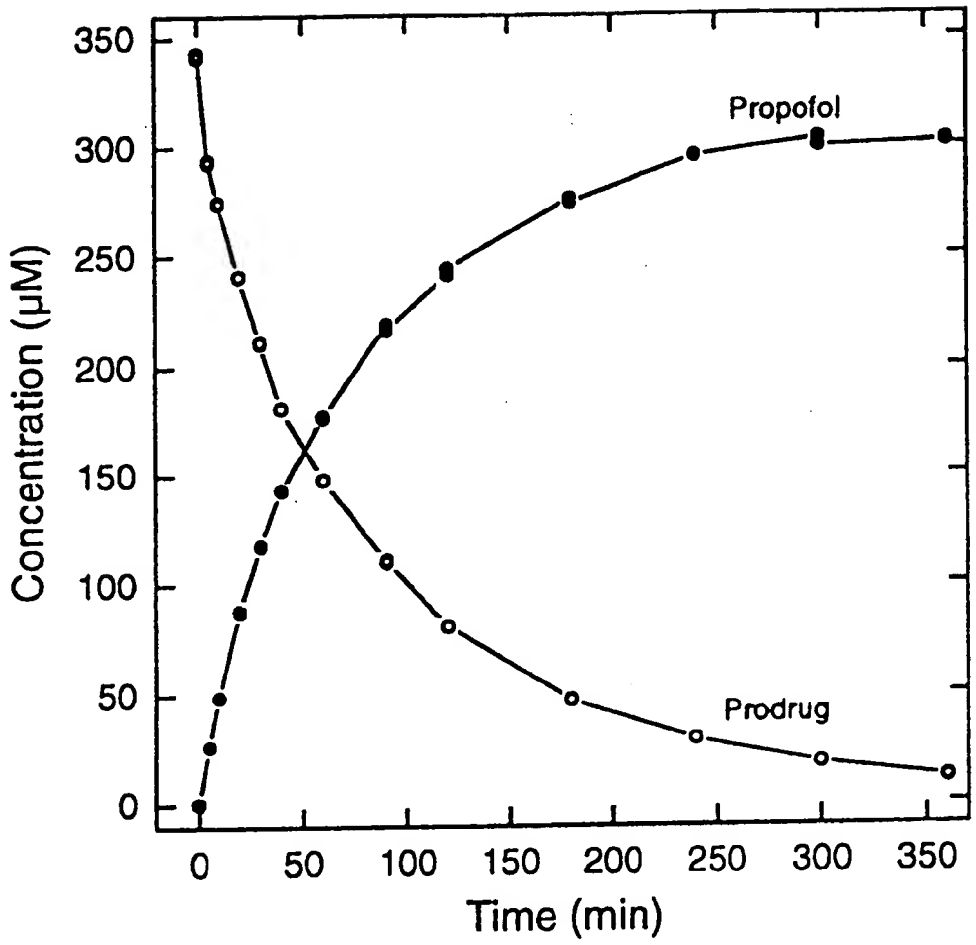

Concentration (μM)
350
300
250
200
150
100
50
0
0
50
100
150
200
250
300
350
Time (min)
Propofol
Prodrug

Figure 1

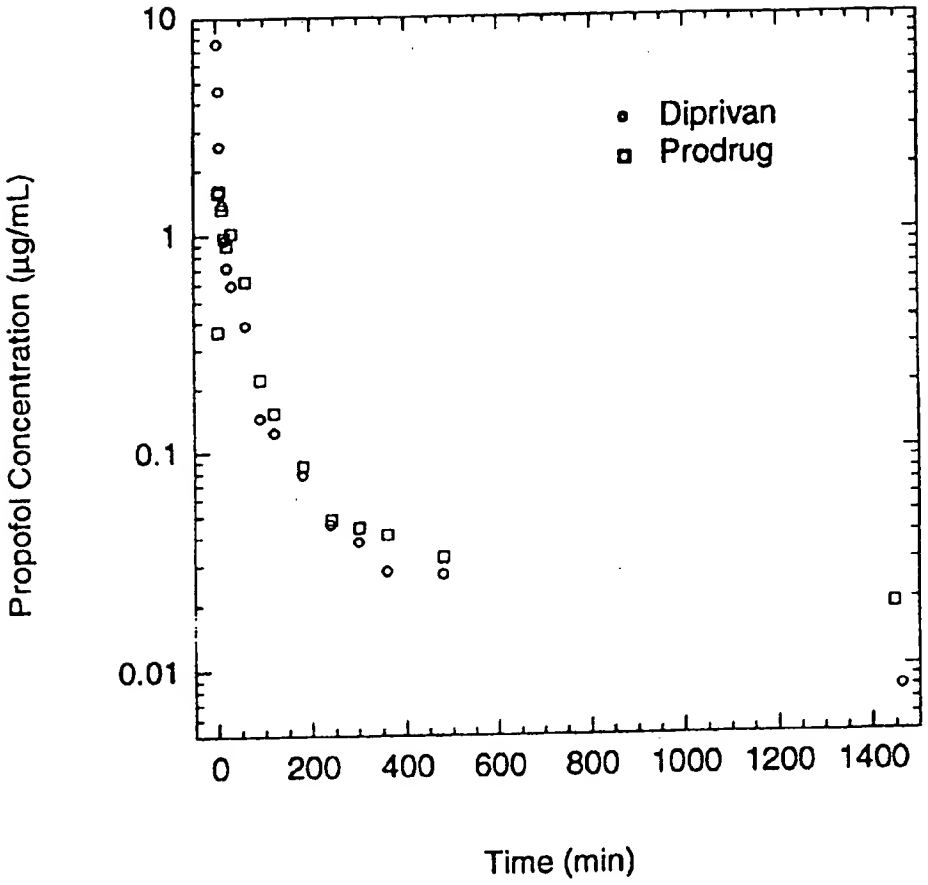

10
1
0.1
0.01
Propofol Concentration (µg/mL)
Diprivan
Prodrug
0
200
400
600
800
1000
1200
1400
Time (min)

Figure 2

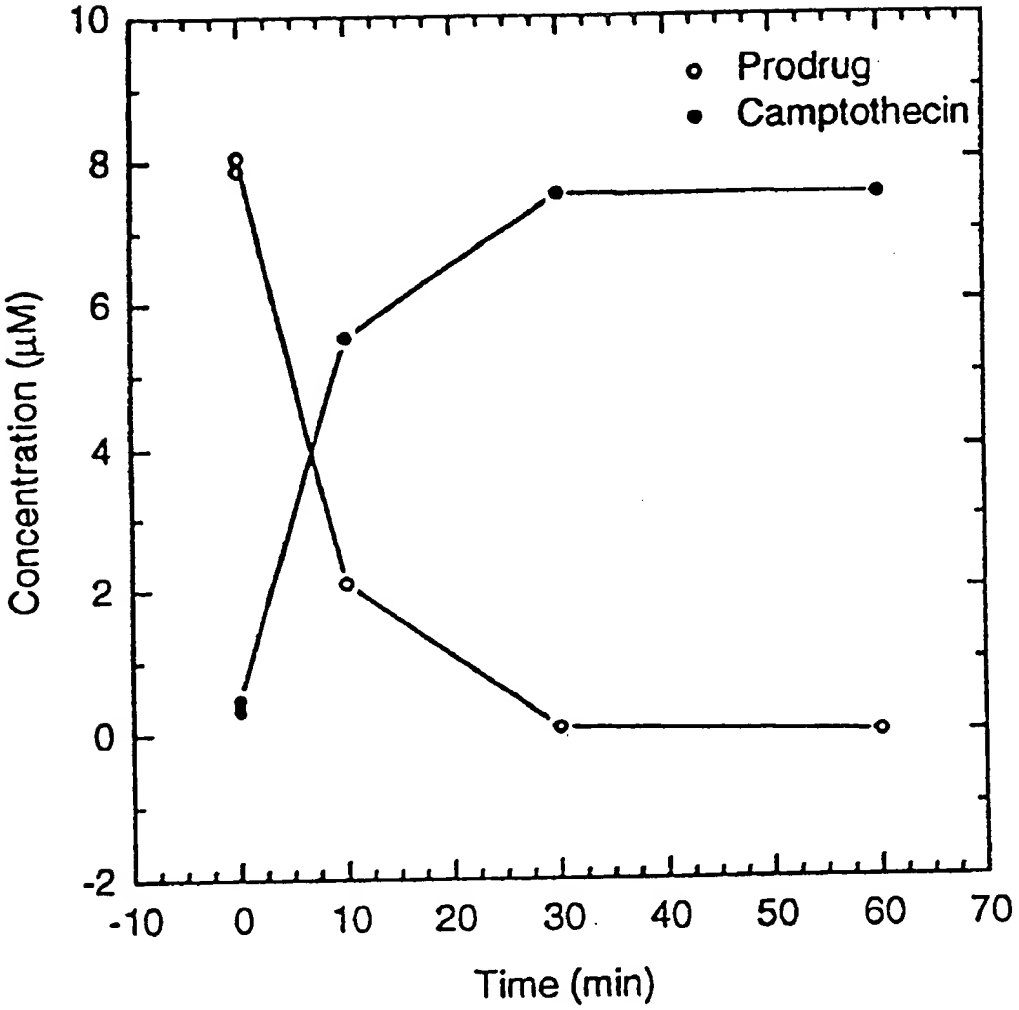

Prodrug
Camptothecin
Concentration (μM)
Time (min)
10
8
6
4
2
0
-2
-10
0
10
20
30
40
50
60
70

Figure 3

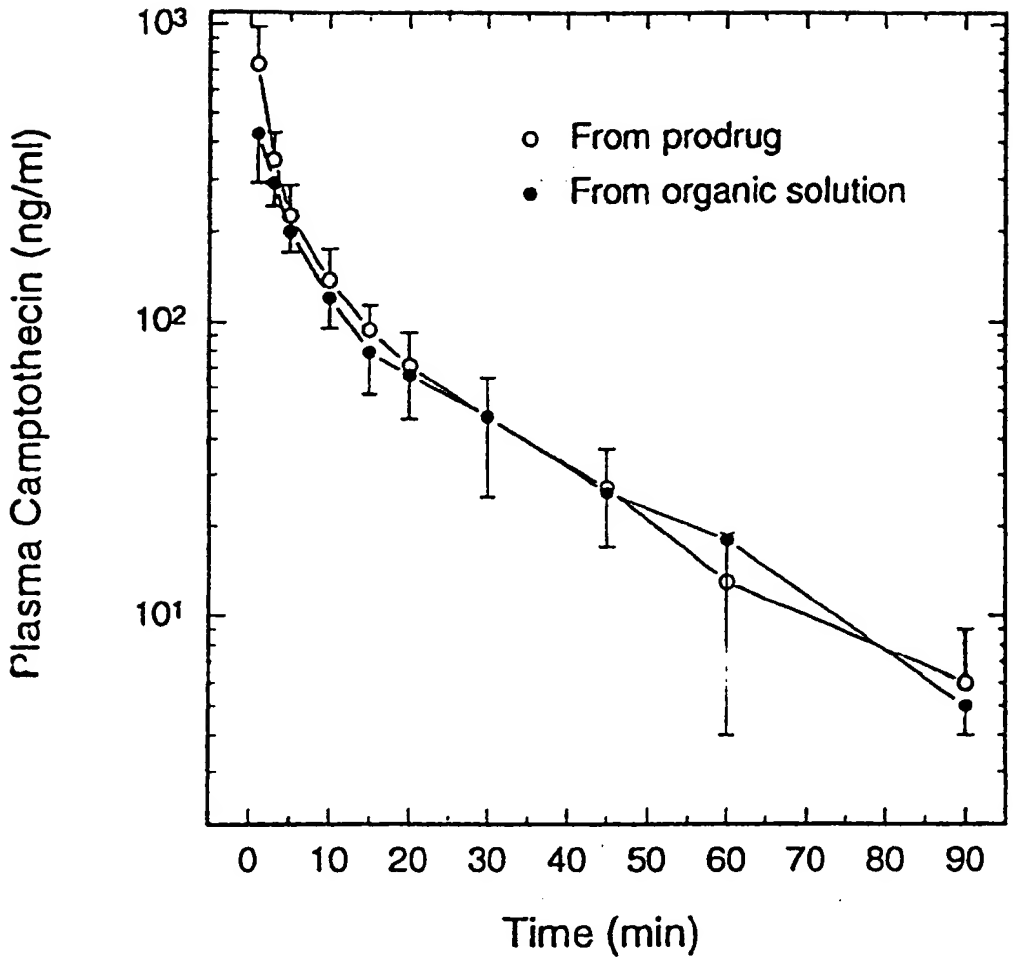

Plasma Camptothecin (ng/ml)
10³
10²
10¹
From prodrug
From organic solution
0
10
20
30
40
50
60
70
80
90
Time (min)

Figure 4

WATER SOLUBLE PRODRUGS OF HINDERED ALCOHOLS

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to novel water-soluble prodrugs of aliphatic or aromatic hindered hydroxyl group containing pharmaceuticals. Particularly, the present invention concerns novel water-soluble phosphonooxymethyl ethers of hindered alcohol and phenol containing pharmaceuticals, such as camptothecin, propofol, etoposide, Vitamin E and Cyclosporin A. The present invention also relates to intermediates used to create the final prodrugs as well as pharmaceutical compositions containing the novel compounds.

2. Background Art

The successful delivery of a pharmaceutical to a patient is of critical importance in the treatment of disorders. However, the use of many clinical drugs with known properties is limited by their very low water solubility. As a result of low water solubility these drugs must be formulated in co-solvent pharmaceutical vehicles, including surfactants. These surfactants have been shown to lead to severe side effects in humans that limit the clinical safety of these drugs and therefore the treatment of several disorders.

For example, camptothecin is a natural product isolated from barks of the Chinese camptotheca tree, *Camptotheca accuminata*. It has been shown to have strong anti-tumor activity in several in vivo animal models including major tumor types such as lung, breast, ovary, pancreas, colon and stomach cancer and malignant melanoma. Camptothecin inhibits the cellular enzyme DNA topoisomerase I and triggers a cascade of events leading to apoptosis and programmed cell death. Topoisomerase I is essential nuclear enzyme responsible for the organization and modulation of the topological feature of DNA so that a cell may replicate, transcribe and repair genetic information.

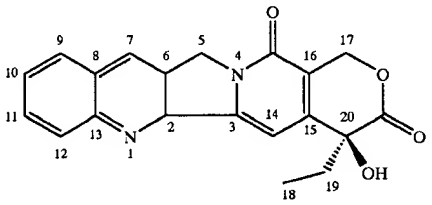
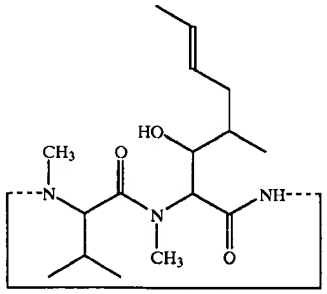


Figure 1 - Camptothecin

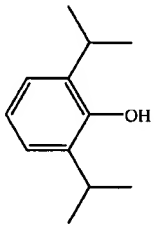
The serious drawback of camptothecin is its very limited water solubility. For biological studies it is necessary to dissolve the compound in a strong organic solvent (DMSO) or to formulate the drug as a suspension in Tween 80:saline which is an undesirable drug formulation for human therapy. Recently two analogs of camptothecin with moderate water solubility have been approved in United States for treatment of advanced ovarian cancer (Hycamtin) and colorectal cancer (Camptosar).

Other drugs, like camptothecin, that have similar problems are cyclosporin A (CsA), propofol, etoposide and Vitamin E (alpha-tocopherol). Like camptothecin, CsA has within its structure a sterically hindered alcohol, a secondary alcohol in this case. CsA is formulated in a CremophorEL/ethanol mixture.



Cycloosporin A

An example of a sterically hindered, poorly water soluble phenol is propofol, an anesthetic.



Profofol (2,6-diisopropylphenol)

Propofol is formulated for i.v. clinical use as a o/w emulsion. Not only is propofol poorly water soluble, but it also causes pain at the site of injection. This pain must be ameliorated by using lidocaine. Due to the fact that it is formulated as an emulsion, it is difficult and questionable to add other drugs to the formulation and physical changes to the formulation such as an increase in oil droplet size can lead to lung embolisms, etc. A water soluble and chemically stable prodrug of propofol would provide several advantages. Such a formulation could be a simple aqueous solution that could be admixed with other drugs. If the prodrug itself was painless, the prodrug may be more patient friendly, and finally there should be no toxicity due to the vehicle. Other poorly water soluble, sterically hindered phenols are the anticancer drug, etoposide and Vitamin E (alpha-tocopherol).

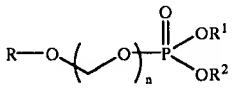
The present invention provides a water soluble form of alcohol and phenol containing drugs such as camptothecin and propofol. With respect to camptothecin, compounds according to the present inventions are phosphonooxymethyl ethers of camptothecin in the form of the free acid and pharmaceutically acceptable salts thereof. The water solubility of the acid and the salts facilitates preparation of pharmaceutical formulations. All of the prodrugs according to the present invention exhibit superior water solubility compared to their respective parent drugs. The methods developed for the compounds of the present invention can be useful for conversion of many other water insoluble medicinal agents having aliphatic or aromatic hindered hydroxyl groups to the water soluble derivatives.

SUMMARY OF THE INVENTION

The invention described herein involves new compositions of matter. The invention relates to the water soluble

phosphonooxymethyl derivatives of alcohol and phenol containing pharmaceuticals represented by the general formula I:

I



The above formula I is the derivative of ROH, wherein ROH represents an alcohol- or phenol-containing drug, such as camptothecin, propofol, etoposide, vitamin E and cyclosporin A. In the above formula I, n represents an integer of 1 or 2. When n is 2, ROH is preferably a phenol-containing pharmaceutical, such as propofol. Also included are some drugs for which injectable forms are not possible due to their inherent poor water solubility. These include danazol, methyltestosterone, iodoquinol and atovaquone. R^1 is hydrogen or an alkali metal ion including sodium, potassium or lithium or a protonated amine or protonated amino acid or any other pharmaceutically acceptable cation. R^2 is hydrogen or an alkali metal ion including sodium, potassium or lithium or a protonated amine or a protonated amino acid or any other pharmaceutically acceptable cation. After intravenous or oral administration, the derivatives according to formula I are converted back to the parent drugs by hydrolysis and/or phosphatase.

Accordingly, it is an object of the present invention to develop derivatives of water insoluble drugs which exhibit good activity and water solubility.

It is another object of the present invention to develop pharmaceutical compositions of these water soluble compounds, which comprises an amount of the compound of formula I and a pharmaceutically acceptable carrier.

It is another object of the present invention to develop drug derivatives having good stability at pH levels suitable for making pharmaceutical formulations, but quickly break down in vivo under physiological conditions, to potentially act as prodrugs.

BRIEF DESCRIPTION OF THE DRAWINGS

The drawings of the present application are explained as follows:

FIG. 1 illustrates an in vitro enzymatic conversion of propofol prodrug to propofol.

FIG. 2 illustrates the blood concentration change of propofol with respect to time from administration of the propofol prodrug or Diprivan® in a dog study.

FIG. 3 illustrates an in vitro enzymatic conversion of camptothecin prodrug to camptothecin.

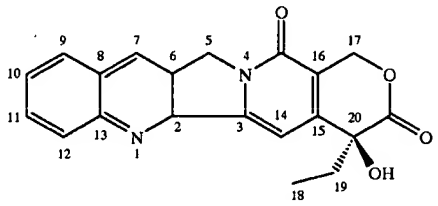
FIG. 4 illustrates the correlation between plasma concentration of camptothecin from the camptothecin prodrug and from camptothecin in organic co-solvents for a rat study.

DETAILED DESCRIPTION OF THE INVENTION

In the present specification, unless otherwise specified or in context, the following definitions apply.

"Phosphono-" means the group —P(O)(OH)2 and "phosphonooxymethoxy" or "phosphonooxymethyl ether" means generically the group —$OCH_2OP(O)(OH)_2$. "Methylthiomethyl" refers to the group —CH_2SCH_3. The present invention also encompasses compounds wherein n=2 such that a "phosphono-di(oxymethyl) ether" generically means the group —$OCH_2OCH_2OP(O)(OH)_2$.

"Camptothecin moiety" denotes moiety containing the twenty carbon camptothecin core framework including two nitrogen atoms and four oxygen atoms as represented by the structural formula shown below with the absolute configuration.



The numbering system shown above is one used in conventional camptothecin derivatives, and is followed throughout the application. For example the notation C20 refers to the carbon atom labeled as "20".

"Camptothecin analogue" refers to a compound having the basic camptothecin core framework. It is to be understood that camptothecin analogues encompass compounds including but not limited to the following compounds: Topotecan, available from SmithKline Beecham, Irinotecan (CPT-11), available from Pharmacia & Upjohn, 9-Aminocamptothecin (9AC), 9-Nitrocamptothecin (9NC), GI 147211C, available from Glaxo Wellcome, and DX-8951f (the previous six camptothecin anologues are currently under clinical investigation and are described in a review conducted by the Pacific West Cancer Fund authored by Claire McDonald (December 1997).

Additionally, several other non-limiting Camptothecin analogues which are herein incorporated by reference are disclosed by Sawada et al., *Current Pharmaceutical Design*, Vol. 1, No. 1, pp 113–132, as well as U.S. Pat. Nos. 5,646,159, 5,559,235, 5,401,747, 5,364,858, 5,342,947, 5,244,903, 5,180,722, 5,122,606, 5,122,526, 5,106,742, 5,053,512, 5,049,668, 4,981,968 and 4,894,456.

Several pharmaceutical compounds including their respective derivatives of camptothecin contain more than one hydroxyl group, for example 10-hydroxycamptothecin, topotecan and several others listed in the above references. It is herein understood that the present invention may be applied to more than one hydroxyl group. This may be accomplished by protecting the additional hydroxyl group prior to derivatization.

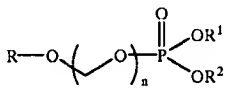
"Phosphono protecting groups" means moieties, which can by employed to block or protect the phosphono functional group. Preferably, such protecting groups are those that can be removed by methods that do not appreciably affect the rest of the molecule. Suitable phosphonooxy protecting groups include for example benzyl (denoted by "Bn"), t-butyl, and allyl groups.

"Pharmaceutically acceptable salt" means a metal or an amine salt of the acidic phosphono group in which the cation does not contribute significantly to the toxicity or biological activity of the active compound. Suitable metal salts include lithium, potassium, sodium, calcium, barium, magnesium, zinc, and aluminum salts. Preferred salts are sodium and potassium salts. Suitable amines salts are for example, ammonia, tromethamine, triethanolamine, ethylenediamine, glucamine, N-methylglucamine, glycine, lysine, ornithine, arginine, ethanolamine, to name but a few. Preferred amine salts are lysine, arginine, N-methylglucamine, and tromethamine salts.

In the specification and in the claims, the term —$OCH_2OP(O)(OH)_2$ is intended to encompass both the

free acid and its pharmaceutically acceptable salts, unless the context indicates specifically that the free acid is intended.

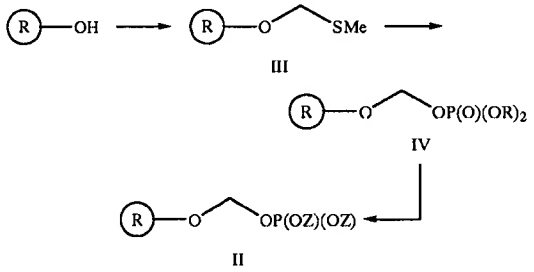
One aspect of the present invention provides for derivatives of alcohol and phenol containing pharmaceuticals as shown in formula I:



I

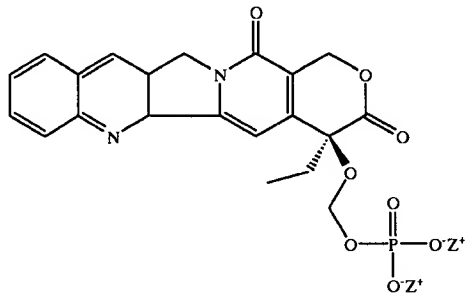
The derivatives according to formula I can be prepared according to the reaction sequence shown in Scheme 1:

Scheme 1



wherein ROH represents an alcohol- or phenol-containing drug, such as camptothecin, propofol, etoposide, vitamin E, cyclosporin A. It is to be understood that the above pathway is just one of several alternate pathways. These alternate pathways will become evident upon review of the following disclosure and examples.

An example of the above Scheme 1 can be illustrated using the compound camptothecin. It is to be understood that these schemes are applicable to other compounds encompassed by formula I of the present invention, such as those listed above. Accordingly, another aspect of the present invention provides camptothecin derivatives of according to formula II:



II

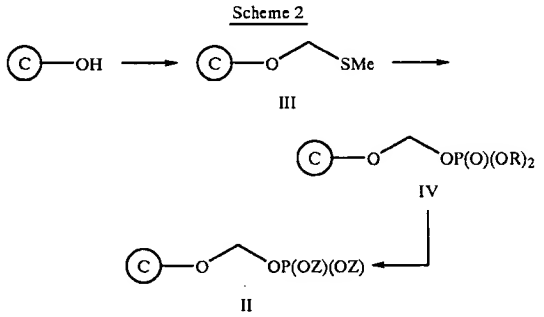
which include the free acid wherein Z is hydrogen and pharmaceutically acceptable salts thereof wherein Z is metal or amine. Alternatively, formula II includes diacids where Z is metal or amine in both occurrences.

The preferred pharmaceutically acceptable salts of a compound of formula II are alkali salts including lithium, sodium, and potassium salts; and amine salts including triethylamine, triethanolamine, ethanolamine, arginine, lysine and N-methylglucamine salts.

The most preferred embodiments of camptothecin derivatives of formula II include the following compounds: (20)-O-phosphonooxymethylcamptothecin, (20)-O-phosphonooxymethylcamptothecin mono- or di-sodium salt, (20)-O-phosphonooxymethylcamptothecin mono or di-potassium salt, (20)-O-phosphonooxymethylcamptothecin mono- or di-arginine salt, (20)-O-phosphonooxymethylcamptothecin mono- or di-lysine salt, (20)-O-phosphonooxymethylcamptothecin mono- or di-N-methylglucamine salt and (20)-O-phosphonooxymethylcamptothecin mono- or di-triethanolamine salt.

Compounds of formula II may be prepared directly from camptothecin (shown as ©-OH) according to the reaction sequence shown in Scheme 2:

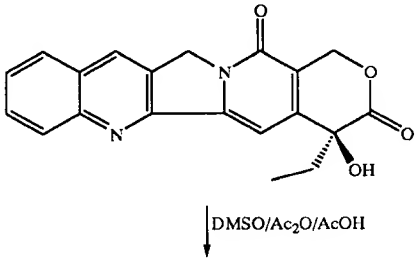
Scheme 2



A compound of formula III (methylthiomethyl ether, MTM ether) may be prepared by treating camptothecin with dimethylsulfoxide/acetic anhydride/acetic acid.

In the second step shown in Scheme 2, the methylthiomethyl ether is converted to the corresponding protected phosphonooxymethyl ether (compound of formula IV). This is accomplished by treating the MTM ether with N-iodosuccinamide and protected phosphate $HOP(O)(OR)_2$. In the third step, the phosphono protecting groups are removed to provide a compound of formula II. For example, a suitable phosphono protecting group(s) is benzyl that may be removed by catalytic hydrogenolysis. The general process of Scheme 2 for the preparation of a compound of formula I is more particularly exemplified in Scheme 3:

Scheme 3



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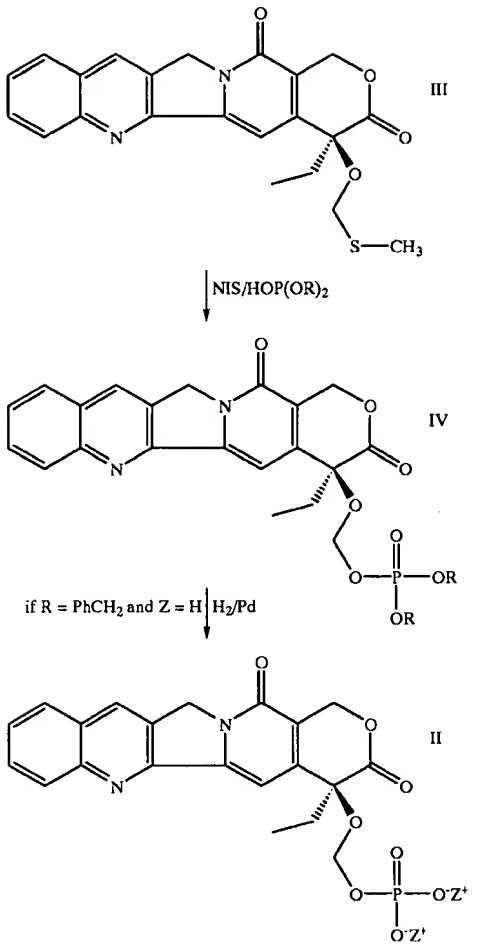


In the first step, the free hydroxy group of the camptothecin is converted to the corresponding methylthiomethyl ether (—OCH_2SCH_3) group. This conversion may be accomplished by reaction with dimethylsulfoxide in the presence of acetic anhydride and acetic acid. This method, commonly known as the Pummer reaction was successfully applied by Bristol-Myers Squibb for methylthiomethylation of taxol (Europ.Pat.0604910A1, Bioorg.Med.Chem.Lett.,6, 1837,1996). The reaction is usually carried out at room temperature, and for 24–72 hours to produce the methylthiomethyl ether.

In the second step of the reaction sequence, the methylthiomethyl ether is converted to the corresponding protected phosphonooxymethyl ether. This well-known conversion was successfully applied by Bristol-Myers Squibb for phosphonooxymethylation of taxol (Europ.Pat.0604910A1, Bioorg.Med.Chem.Lett.,6,1837,1996). Thus, a compound of formula III is treated with N-iodosuccinamide and protected phosphoric acid such as dibenzyl phosphate. The reaction is carried out in an inert organic solvent such as tetrahydrofuran and halogenated hydrocarbon such as methylene chloride and in the presence of molecular sieves. Reaction is carried out at room temperature. N-iodosuccinimide and protected phosphoric acid are used in excess (3–5 equivalents) relative to the methylthiomethyl ether.

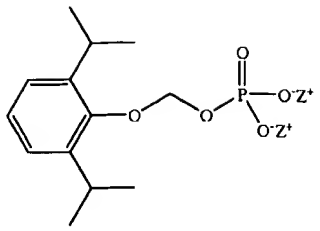
In the third step of the reaction sequence, the phosphono protecting groups are removed. The deblocking is accomplished by conventional methods well known in the art such as acid- or base-catalyzed hydrolysis, hydrogenolysis, reduction, and the like. For example, catalytic hydrogenolysis can be used to remove the benzyl phosphono-protecting group. Deprotecting methodologies may be found in standard texts, such as T. W. Green and P.G.M. Wutz, Protective groups in organic sythesis, J. Wiley publishers, New York, N.Y., 1991, pp. 47–67.

The base salts of a compound of formula II may be formed by conventional techniques involving contacting a compound of formula II free acid with a metal base or with an amine. Suitable metal bases include hydroxides, carbonates and bicarbonates of sodium, potassium, lithium, calcium, barium, magnesium, zinc, and aluminum; and suitable amines include triethylamine, ammonia, lysine, arginine, N-methylglucamine, ethanolamine, procaine, benzathine, dibenzylamine, tromethamine (TRIS), chloroprocaine, choline, diethanolamine, triethanolamine and the like. The base salts may be further purified by chromatography followed by lyophilization or crystallization.

Compounds of the present invention are phosphonooxymethyl ether pharmaceuticals such as camptothecin, propofol, etoposide, tocopherol, etc. The pharmaceutically acceptable salt forms exhibit improved water solubility over parent compounds thereby allowing more convenient pharmaceutical formulations. Without being bound by theory, it is believed that the phosphonooxymethyl ethers of the present invention are prodrugs of the parent pharmaceuticals; the phosphono-oxyethyl moiety being cleaved upon contact with phosphatase in vivo to generate subsequently the parent compound. As shown above, compounds of the instant invention are effective pharmaceutical or therapeutic agents.

For example, compounds of formula II of the present invention may be used in a manner similar to that of camptothecin. The structure of the camptothecin prodrug is shown above. Therefore, an oncologist skilled in the art of cancer treatment will be able to ascertain, without undue experimentation, an appropriate treatment protocol for administering a compound of the present invention. The dosage, mode and schedule of administration of compounds of this invention are not particularly restricted, and will vary with the particular compound employed. Thus a compound of the formula II may be administrated via any suitable route of administration, preferable parenterally; the dosage may be, for example, in the range of about 0.1 to about 100 mg/kg of body weight, or about 5 to 500 mg/m2. Compounds of formula II may also be administrated orally; oral dosage may be in the range of about 5 to about 500 mg/kg of body weight. The actual dose used will vary according to the particular composition of formulated, the route of administration, and the particular site, host and type of tumor being treated. Many factors that modify the action of the drug will be taken into account in determining the dosage including age, sex, diet and the physical conditions of the patient.

Another example is the propofol prodrug according to formula I of the present invention. The structure of the propofol prodrug is shown below:



Propofol Prodrug

In the above formula for the propofol prodrug, Z is the same as defined above for formula II. Therefore, an anesthesiologist skilled in the art of anesthesia will be able to ascertain, without undue experimentation, an appropriate treatment protocol for administering a compound of the present invention. The dosage, mode and schedule of administration of compounds of this invention are not particularly restricted, and will vary with the particular compound employed. Thus, a compound of formula I such as the propofol prodrug may be administered via any suitable route of administration, preferably parenterally; the dosage may be, for example, in the range of 0.5 to 10 mg/kg administered according to procedures for induction of general anesthesia or maintenance of general anesthesia. Alternatively, the compound of formula I may be administered by parenteral infusion, the dosage may be, for example, in the range of 2 μg/kg/min to 800 μg/kg/min administered according to procedures for maintenance of general anesthesia, initiation and maintenance of MAC sedation or initiation and maintenance of ICU sedation.

The present invention also provides pharmaceutical compositions containing a pharmaceutically effective amount of compound of formula I in combination with one or more pharmaceutically acceptable carriers, excipients, diluents or adjuvants. For example, compounds of the present invention may be formulated in the form of tablets, pills, powder mixtures, capsules, injectables, solutions, suppositories, emulsions, dispersions, food premix, and in other suitable forms. They may also be manufactured in the form of sterile solid compositions, for example, freeze-dried and, if desired, combined with other pharmaceutically acceptable excipients. Such solid compositions can be reconstituted with sterile water, physiological saline, or a mixture of water and an organic solvent, such as propylene glycol, ethanol, and the like, or some other sterile injectable medium immediately before use of parenteral administration.

Typical of pharmaceutically acceptable carriers are, for example, manitol, urea, dextrans, lactose, non-reducing sugars, potato and maize starches, magnesium stearate, talc, vegetable oils, polyalkylene glycols, ethyl cellulose, poly (vinyl-pyrrolidone), calcium carbonate, ethyloleate, isopropyl myristate, benzyl benzoate, sodium carbonate, gelatin, potassium carbonate, silicic acid. The pharmaceutical preparation may also contain non toxic auxiliary substances such as emulsifying, preserving, wetting agents, and the like as for example, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene monostearate, glyceryl tripalmitate, dioctyl sodium sulfosuccinate, and the like.

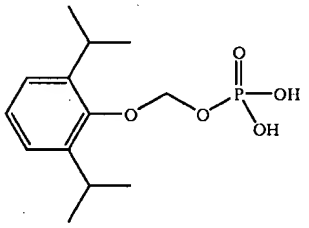
In the following experimental procedures, all temperatures are understood to be in Centigrade (C) when not specified. The nuclear magnetic resonance (NMR) spectral characteristics refer to chemical shifts (δ) expressed in parts per million (ppm) versus tetramethylsilane (TMS) as reference standard. The relative area reported for the various shifts in the proton NMR spectral data corresponds to the number of hydrogen atoms of a particular functional type in the molecule. The nature of the shifts as to multiplicity is reported as broad singlet (bs), broad doublet (bd), broad triplet (bt), broad quartet (bq), singlet (s), multiplet (m), doublet (d), quartet (q), triplet (t), doublet of doublet (dd), doublet of triplet (dt), and doublet of quartet (dq). The solvents employed for taking NMR spectra are acetone-d6 (deuterated acetone) DMSO-d6 (perdeuterodimethylsulfoxide), D_2O (deuterated water), $CDCl_3$ (deuterochloroform) and other conventional deuterated solvents.

The abbreviations used herein are conventional abbreviations widely employed in the art. Some of which are: MS (mass spectrometry); HRMS (high resolution mass spectrometry); Ac (acetyl); Ph (phenyl); FAB (fast atom bombardment); min (minute); h or hrs (hour(s)); NIS (N-iodosuccinimide); DMSO (dimethylsulfoxide); THF (tetrahydrofuran).

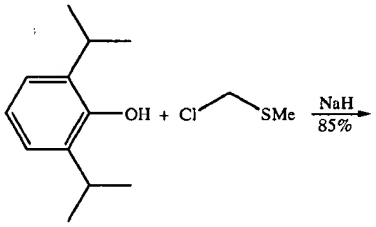
The following examples are provided to illustrate the synthesis of representative compounds of the instant invention and are not to be construed as limiting the scope of the invention in any manner. One skilled in the art will be able to adapt these methods, without undue experimentation, to the synthesis of compounds within the scope of this invention but not specifically disclosed. For example, in the following examples, specific salts are employed, however, these salts are not to be construed as limiting. An example of this situation is the repeated use of a silver salt of dibenzylphosphate. Tetralkyl ammonium salts, such as tetramethyl ammonium salts or other alkali metal salts may be used in lieu of the silver salt.

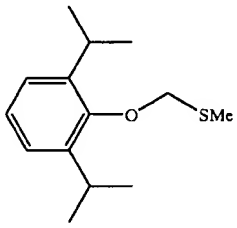
EXAMPLES

I. Synthesis of O-Phosphonooxymethylpropofol



Ia. Synthesis of O-methylthiomethylpropofol:





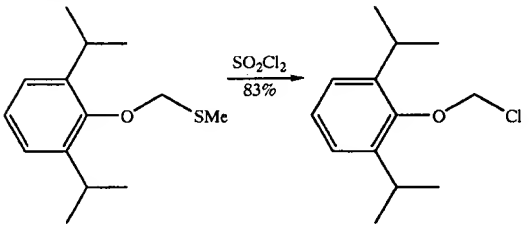
To a stirred suspension of sodium hydride (150 mg, 6.2 mmol) in dry HMPA (10 mL), kept under an argon

atmosphere, was added dropwise propofol (1.1 mL of 97%, 5.7 mmol) over 15 minutes. The reaction mixture was then stirred at room temperature for an additional 30 minutes. To this mixture was added dropwise chloromethyl methyl sulfide (550 μl of 95%, 6.2 mmol) and then stirred at room temperature. After 20 hours, the reaction mixture was partitioned with stirring between water (10 mL) and benzene (20 mL). The aqueous layer was separated and extracted with benzene (10 mL). The benzene fractions were combined, washed with water (2×3 mL), dried over sodium sulfate, and evaporated under reduced pressure. The resulting oily residue was subjected to column chromatography (silica gel, hexane, then 4:1 hexane/chloroform) to give 1.15 g (85% yield) of the title compound as a colorless oil.

EIMS: [M+], m/z 238.

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.24 (d, J=6.9 Hz, 12H), 2.37 (s, 3H), 3.37 (hept, J=6.9 Hz, 2H), 4.86 (s, 2H), 7.12 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$, δ): 15.40, 23.98, 26.68, 78.12, 124.04, 125.05, 141.74, 152.20.

Ib. Synthesis of O-chloromethylpropofol:

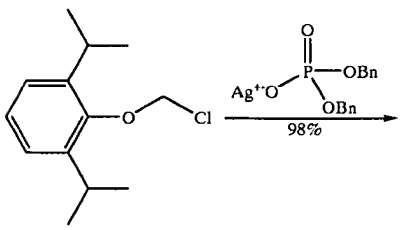


To a stirred solution of O-methylthiomethylpropofol (3.00 g, 12.5 mmol) in dry methylene chloride (30 mL), kept under an argon atmosphere, was added a 1M solution of SO_2Cl_2 in dry methylene chloride (12.2 mL, 12.2 mmol) at 5° C. over five minutes. The reaction mixture was stirred for 10 minutes at the same temperature and then for three hours at room temperature. The solvent was evaporated under reduced pressure and the brown residual oil was purified by flash column chromatography (silica gel, 1:20 hexane/ethyl acetate) to give 2.36 g (83% yield) of the title compound as a yellow oil.

CIMS (NH_3): $[M]^+$, m/z 226, $[MH+NH_3]+$, m/z 244.

^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.22 (d, J=6.9 Hz, 12H), 3.35 (hept, J=6.9 Hz, 2H), 5.76 (s, 2H), 7.15 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ)23.93, 26.84, 83.34, 124.34, 125.95, 141.34, 150.93.

Ic. Synthesis of O-phosphonooxymethylpropofol dibenzyl ester (route-1):



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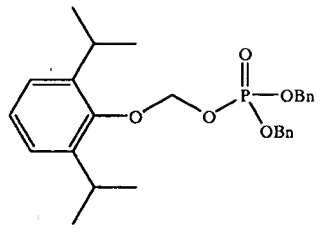
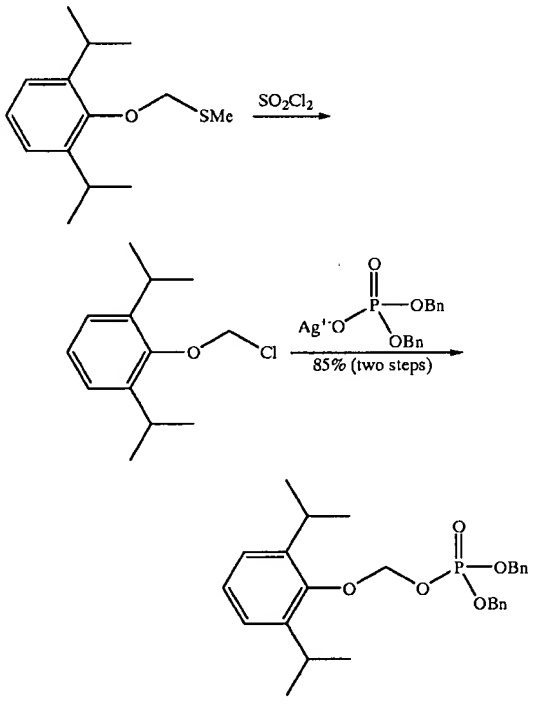


A mixture of O-chloromethylpropofol (2.20 g, 9.7 mmol), silver dibenzylphosphate (3.85 g, 10.0 mmol) and dry toluene (50 mL) was refluxed under an argon atmosphere for 45 minutes. The mixture was cooled down to room temperature and filtered. After the solvent was evaporated in vacuo, the oily residue was purified by silica gel flash column chromatography (9:1 hexane/ethyl acetate and then 1:1 hexane/ethyl acetate) to give 4.43 g (98% yield) of the title compound as a yellow oil.

CIMS (NH_3): $[MH]^+$, m/z 469, $[MH+NH3]^+$, m/z 486.

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.17 (d, J=6.8 Hz, 12H), 3.33 (hept, J=6.9 Hz, 2H), 5.00 (d, J=7.8 Hz, 2H), 5.01 (d, J=7.8 Hz, 2H), 5.42 (d, J=9.9 Hz, 2H), 7.12 (m, 3H), 7.32 (m, 10H) . ^{13}C NMR (75 MHz, $CDCl_3$, δ): 23.79, 26.57, 69.15, 69.23, 94.14, 94.20, 124.07, 125.62, 127.70, 128.44, 135.42, 135.51, 141.50, 151.07.

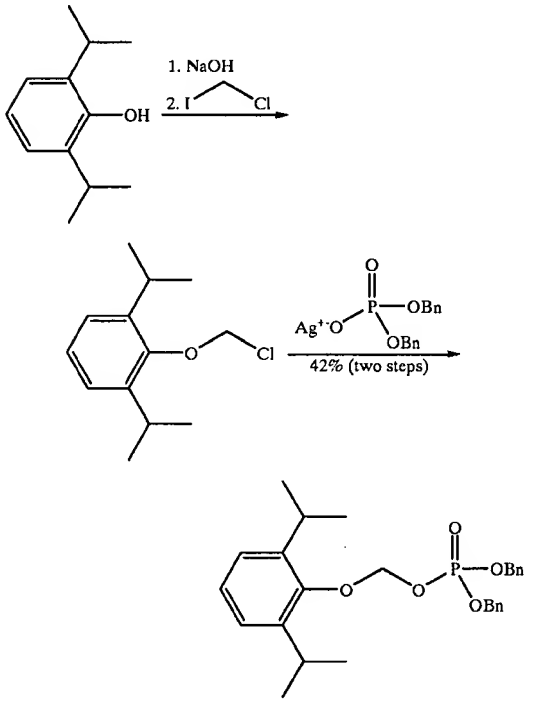
Ic. Synthesis of O-phosphonooxymethylpropofol dibenzyl ester (alternate route-1):



To a stirred solution of O-methylthiomethylpropofol (1.45 g, 6.08 mmol) in dry methylene chloride (15 mL) under an argon atmosphere at 0–5° C. was added a 1M solution of SO_2Cl_2 in dry methylene chloride (6.5 mL, 6.5 mmol) over five minutes. The reaction mixture was stirred for 10 minutes at 5° C. and three hours at room temperature. Then the solvent was evaporated under reduced pressure. The residual

oil was dissolved in toluene (ACS-grade, 20 mL); silver dibenzylphosphate (3.50 g, 9.1 mmol) was added, and the resulting mixture was refluxed for 45 minutes. The brown reaction mixture was cooled down to room temperature and filtered. After the solvent was evaporated in vacuo, the oily residue was purified by silica gel flash column chromatography (9:1 hexane/ethyl acetate, then 1:1 hexane/ethyl acetate) to give 2.41 g (85% yield) of the title compound as a yellow oil. This product had the same R_f (TLC) and ^1H NMR spectrum (300 MHz, $CDCl_3$) as an authentic sample.

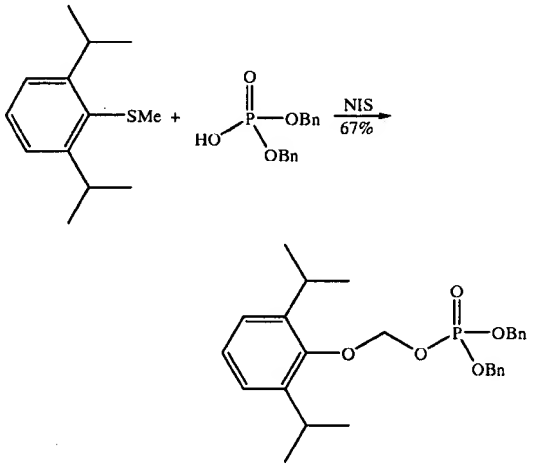
Ic. Synthesis of O-phosphonooxymethylpropofol dibenzyl ester (alternate route-2):



To a stirred suspension of sodium hydride (41 mg of 60% dispersion in mineral oil, 1.02 mmol) in dry dimethoxyethane (1.5 mL) under an argon atmosphere was added dropwise propofol (200 μl of 97%, 1.04 mmol) over 5 minutes and the resulting mixture was stirred for an additional 15 minutes. The resulting homogeneous solution was added dropwise to a stirred solution of chloroiodomethane (4.0 mL, 53 mmol) in dry dimethoxyethane (4 mL) over 15 minutes. This reaction mixture was stirred for two hours, filtered, and then the solvent and the excess of chloroiodomethane were evaporated. The residual oil was dissolved in toluene (HPLC-grade, 10 mL). To this solution was added silver dibenzylphosphate (400 mg, 1.04 mmol), and the resulting mixture was refluxed for 10 minutes. After the reaction mixture was cooled down to room temperature and filtered, the solvent was evaporated in vacuo. The oily residue was purified by silica gel flash column chromatography (9:1 hexane/ethyl acetate and then 1:1 hexane/ethyl acetate) to give 205 mg (42% yield) of the title compound as a yellow oil. This product had the same Rf (TLC) and ^1H NMR spectrum (300 MHz, $CDCl_3$) as an authentic sample.

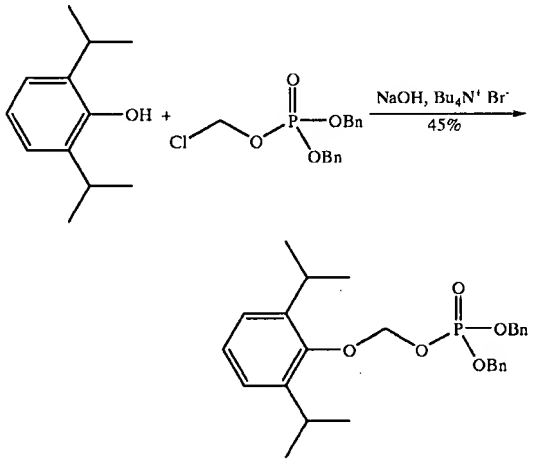
Further to the above reaction Ic (alternate route-2) it is understood that other reagents may be used depending on the desired compound. For example, when, a compound of formula I wherein n=2 is desired, the chloroiodomethane may be substituted with a compound such as X—CH2—O—CH2—Cl, wherein X is a good leaving group.

Ic. Synthesis of O-phosphoncoxymethylpropofol dibenzyl ester (alternate route-3):



To a stirred solution of O-methylthiomethylpropofol (91 mg, 0.38 mmol) in dry methylene chloride (2 mL) under an argon atmosphere were added powdered, activated 4 Å molecular sieves (100 mg), and then a solution of dibenzylphosphate (127 mg, 0.45 mmol) and N-iodosuccinimide (102 mg of 95%, 0.43 mmol) in tetrahydrofuran (2 mL). The reaction mixture was stirred at room temperature for one hour, filtered, and diluted with methylene chloride (30 mL). The resulting solution was washed with a solution of sodium thiosulfate (2 mL of a 1M solution), a saturated solution of sodium bicarbonate (3 mL), brine (5 mL), dried over a mixture of sodium sulfate and magnesium sulfate, filtered, and concentrated in vacuo. The oily residue was purified by silica gel flash column chromatography (1:1 hexane/ethyl acetate) to give 120 mg (67% yield) of the title compound as a yellow oil. This product had the same R_f (TLC) and ^1H NMR spectrum (300 MHz, $CDCl_3$) as an authentic sample.

Ic. Synthesis of O-phosphonooxymethylpropofol dibenzyl ester (alternate route-4):

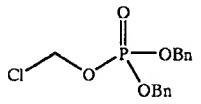


To a solution of propofol (38 mg of 97%, 0.21 mmol) in methylene chloride (1 mL) was added tetrabutylammonium bromide (10 mg, 0.03 mmol) and a solution of sodium

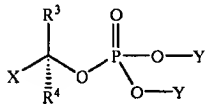
hydroxide (40 mg, 1 mmol) in water (0.2 mL). The heterogeneous mixture was stirred for 15 minutes. Then a solution of chloromethyl dibenzylphosphate (104 mg, 0.32 mmol) in methylene chloride (1 mL) was added and the reaction mixture was stirred vigorously for eight hours.

The mixture was then diluted with methylene chloride (10 mL), washed with water (2 mL), dried over sodium sulfate, filtered, and evaporated in vacuo. The oily residue was purified by silica gel flash column chromatography (hexane, 20:1 hexane/ethyl acetate, and 10:1 hexane/ethyl acetate) to give 44 mg (45% yield) of the title compound as a yellow oil. This product had the same R_f (TLC) and ^1H NMR spectrum (300 MHz, $CDCl_3$) as an authentic sample.

Further to the above reaction Ic (alternate route-4) it is to be understood that the reagent:

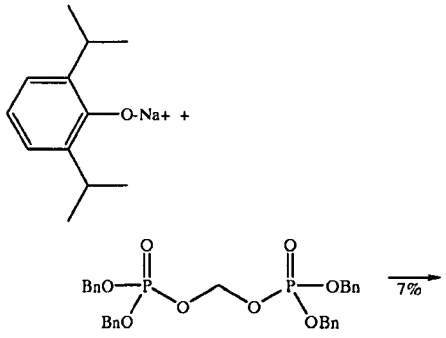


can be generically represented by the following formula:



wherein X represents a leaving group, R3 and R4 are each a hydrogen atom, an organic group or an inorganic group and Y is a phosphate protecting group. Examples of leaving groups include chlorine, bromine, iodine, tosylate or any other suitable leaving group. Examples of phosphate protecting groups include protecting groups that temporarily block the reactivity of the phosphate group and permit selective displacement with the nucleophilic displacement reaction. Examples of such blocking groups include but are not limited to benzyl, allyl, tertiary butyl and isopropyl, ethyl and β-cyanoethyl.

Ic. Synthesis of O-phosphonooxymethylpropofol dibenzyl ester (alternate route-5):



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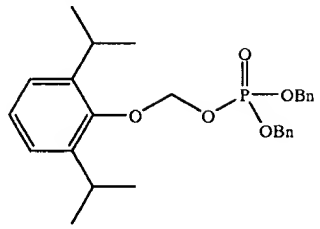
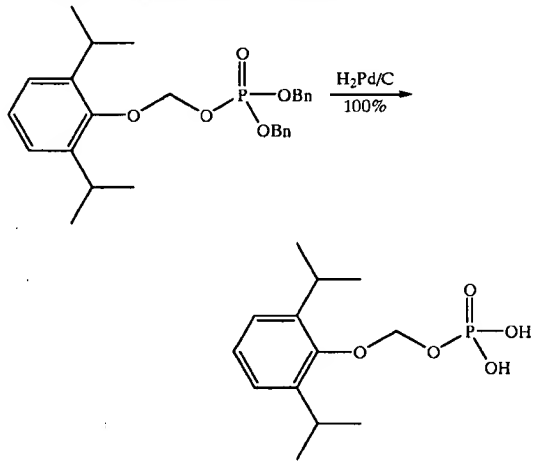


To a stirred suspension of sodium hydride (36 mg of a 60% dispersion in mineral oil, 0.91 mmol) in dry dimethoxyethane (2 mL) under an argon atmosphere was added dropwise propofol (172 μl of 97%, 0.90 mmol) over five minutes. The resulting mixture was stirred at room temperature for an additional 20 minutes. To the mixture was then added the solution of formaldehyde bis-(dibenzylphosphono)acetal (500 mg, 0.88 mmol) in dry dimethoxyethane (3 mL). The reaction mixture was stirred at room temperature for 20 hours and then at 70° C. for 2.5 hours. The mixture was then filtered and the solvent was evaporated in vacuo. The oily residue was purified by silica gel flash column chromatography (hexane, 10:1 hexane/ethyl acetate, and then 1:1 hexane/ethyl acetate) to give 29 mg (7% yield) of the title compound as a yellow oil. This product had the same R_f(TLC) and ^1H NMR spectrum (300 MHz, $CDCl_3$) as an authentic sample.

Id. Synthesis of O-phosphonooxymethylpropofol:

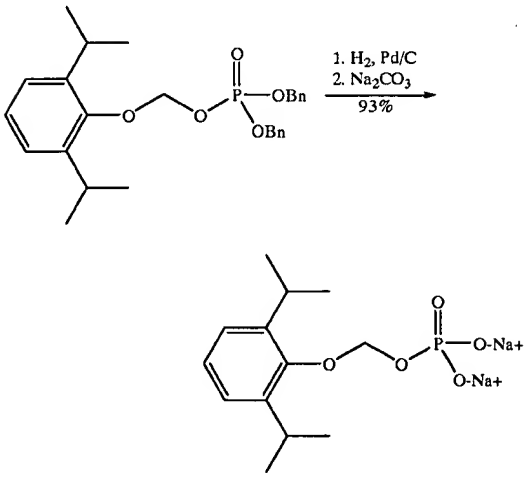


To a solution of O-phosphonooxymethylpropofol dibenzyl ester (115 mg, 0.245 mmol) in methanol (10 mL) was added palladium on carbon (10%, 20 mg). This mixture was stirred under an atmosphere of hydrogen (1 atm) for 1.5 hour. The catalyst was removed by filtration through Celite, and the filtrate was evaporated at reduced pressure to give 70.5 mg (100% yield) of the title compound as a colorless oil, unstable on standing at room temperature.

FABMS-(GLY): $[M-H]^-$, m/z 287.

^1H NMR (300 MHz, acetone-d_6, δ): 1.19 (d, J=6.8 Hz, 12H), 3.46 (sext, J=6.8 Hz, 2H), 5.45 (d, J=9.7 Hz, 2H), 7.15 (m, 3H).^{13}C NMR (75 MHz, acetone-d_6, δ): 24.2178, 27.1496, 94.63, 94.65, 124.08, 126.30, 142.46, 152.32.

Ie. Synthesis of O-phosphonooxymethylpropofol disodium salt:

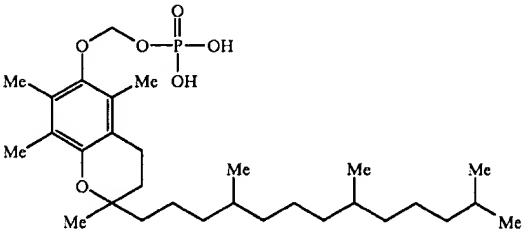


To a solution of O-phosphonooxymethylpropofol dibenzyl ester (1.05 g, 2.24 mmol) in tetrahydrofuran (100 mL) was added water (5 mL) and palladium on carbon (10%, 300 mg). This mixture was stirred under hydrogen (1 atm) for one hour. The catalyst was removed by filtration through Celite, and the filtrate was treated with a solution of sodium carbonate hydrate (263 mg in 3 mL of water, 2.12 mmol). THF was evaporated under reduced pressure and the residual water solution was extracted with ether (3×3 mL). The aqueous layer was evaporated to dryness (argon stream or rotary evaporator) and the resulting solid was dried overnight in vacuo, washed with ether (4×4 mL), hexane (2×4 mL), and again dried in vacuo to provide 655 mg (93% yield) of the title compound as a white powder.

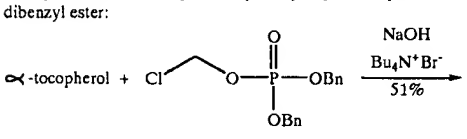
FABMS-(GLY): [M-2Na+H]-, m/z 287.

^{1}H NMR (300 MHz, D_2O, δ): 1.22 (d, J=7.0 Hz, 12H), 3.46 (hept, J=6.9 Hz, 2H), 5.27 (d, J=7.5 Hz, 2H), 7.28 (m, 3H).

II. Synthesis of O-Phosphonooxymethyl-alpha-tocopherol



IIa. Synthesis of O-Phosphonooxymethyl-alpha-tocopherol dibenzyl ester:



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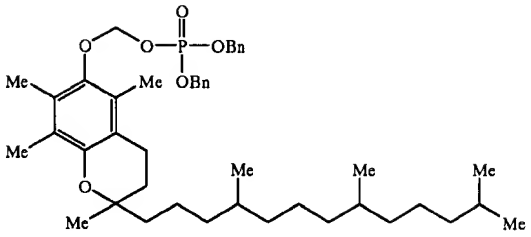
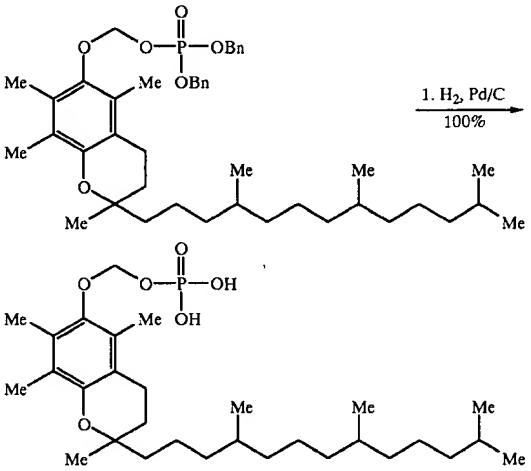


To a solution of chloromethyl dibenzylphosphate (323 mg, 0.98 mmol), alphatocopherol (409 mg of 97%, 0.92 mmol), and tetrabutylammonium bromide (301 mg, 0.92 mmol) in benzene (5 mL) was added an aqueous solution of sodium hydroxide (150 mg in 0.2 mL of water, 3.7 mmol). The resulting reaction mixture was vigorously stirred at room temperature for two hours under an argon atmosphere. The mixture was then diluted with benzene (10 mL), washed with water (3×3 mL), dried over magnesium sulfate, filtered, and evaporated under reduced pressure. The brown oily residue was purified by silica gel flash column chromatography (10:1 hexane/ethyl acetate) to give 336 mg (51% yield) of the title compound as a yellow oil.

FABMS+(NBA) : [M]$^+$, m/z 720.

^{1}H NMR (500 MHz, $CDCl_3$, δ): 0.85 (m, 12H), 1.21 (s, 3H), 1.27 (m, 24H), 1.75 (m, 2H), 2.06 (s, 3H), 2.11 (s, 3H), 2.14 (s, 3H), 2.54 (t, J=6.8 Hz, 2H), 4.97 (m, 4H), 5.20 (d, J=9.3 Hz, 2H), 7.31 (m, 10H).

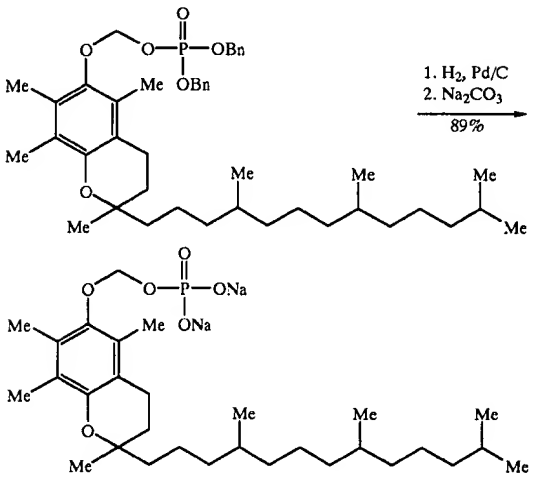
IIb. Synthesis of O-Phosphonooxymethyl-alpha-tocopherol:



To a solution of O-phosphonooxymethyl-alpha-tocopherol dibenzyl ester (88 mg, 0.12 mmol) in tetrahydrofuran (10 mL) was added palladium on carbon (10%, 15 mg). The mixture was stirred under an atmosphere of hydrogen (1 atm) for 10 minutes (the reaction was complete after 5 minutes as judged by TLC). The catalyst was removed by filtration through Celite, the filtrate was evaporated at reduced pressure, and then dried in vacuo. The title compound was obtained in an amount of 70 mg (100% yield) as a brownish oil, which was unstable at room temperature.

FABMS+(NBA): [M]$^+$, m/z 540, [M+Na]$^+$, m/z 563; (NBA+Li): [M+Li]$^+$, m/z 547

IIc. Synthesis of O-Phosphonooxymethyl-alpha-tocopherol disodium salt:

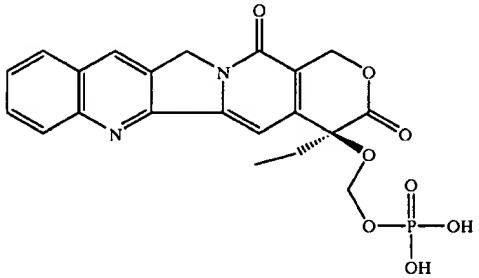


To a solution of O-phosphonooxymethyl-alpha-tocopherol dibenzyl ester (100 mg, 0.14 mmol) in tetrahydrofuran (10 mL) was added palladium on carbon (10%, 18 mg). The mixture was stirred under an atmosphere of hydrogen (1 atm) for 5 minutes. The catalyst was removed by filtration through Celite, the filtrate was evaporated at room temperature at reduced pressure, and the resulting residue was dissolved in ether (2 mL). The ether solution was then treated with an aqueous solution of sodium hydroxide (11.2 mg in 100 mL of water, 0.28 mmol), and the resulting mixture was stirred at room temperature for 10 min. The ether phase was removed and the aqueous phase was washed with ether (3×3 mL) and then dried in vacuo for 20 hours to give 73 mg (89% yield) of the title compound as a gray solid.

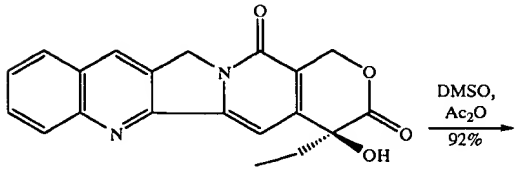
FABMS+(TG/G): $[MH]^+$, m/z 585, $[M+Na]^+$, m/z 607

The synthesis of water soluble derivatives of camptothecin will also be further detailed as follows:

III. Synthesis of 20-O-Phosphonooxymethylcamptothecin



IIIa. Synthesis of 20-O-methylthiomethylcamptothecin:



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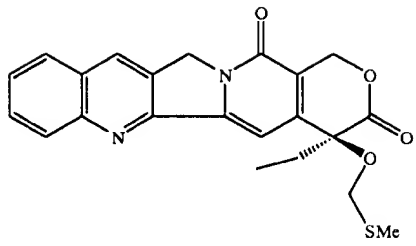


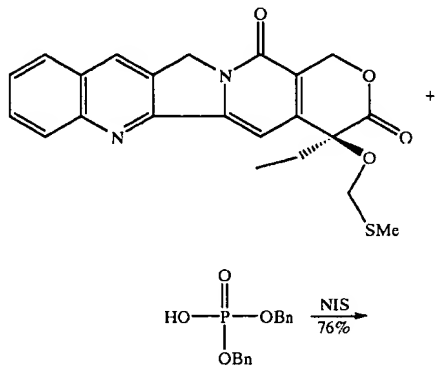
To a suspension of camptothecin (5.0 g, 14.3 mmol) in dimethylsulfoxide (250 mL) was added acetic anhydride (125 mL) and acetic acid (35 mL). The heterogeneous mixture was vigorously stirred at room temperature for 24 hours, poured into ice (800 mL), stirred for 30 minutes, and then extracted with methylene chloride (4×100 mL). The combined methylene chloride extracts were washed with water (2×100 mL) and dried over magnesium sulfate. The methylene chloride was removed at reduced pressure to give a brownish solid. The solid was dissolved in a minimum volume of methylene chloride. This solution was filtered and diluted with a 10-fold excess of hexane and then kept overnight in the refrigerator. The precipitated solid was filtered off, washed several times with hexane, and dried to give 5.38 g (92% yield) of the title compound as a light brown powder. α^{D}_{20}-123.6° (c 0.55, $CHCl_3$).

FABMS+(NBA): $[MH]^+$, m/z 409.

^1H NMR (400 MHz, $CDCl_3$, δ): 0.93 (t, J=7.2 Hz, 3H), 2.11 (sext, J=7.6 Hz, 1H), 2.29 (sext, J=7.6 Hz, 1H), 2.30 (s, 3H), 4.58 (s, 2H), 5.33 (s, 2H), 5.40 (d, J=17.2 Hz, 1H), 5.62 (d, J=17.3 Hz, 1H), 7.48 (s, 1H), 7.69 (t, J=7.1 Hz, 1H), 7.86 (t, J=7.1 Hz, 1H), 7.96 (d, J=8.1 Hz, 1H), 8.25 (d, J=8.5 Hz, 1H), 8.42 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 7.76, 14.89, 33.90, 49.92, 66.68, 71.02, 76.57, 97.51, 122.63, 128.02, 128.09, 128.30, 129.71, 130.64, 131.11, 145.14, 146.10, 148.88, 152.27, 157.43, 169.34, 169.73.

IIIb. Synthesis of 20-O-phosphonooxymethylcamptothecin dibenzyl ester:



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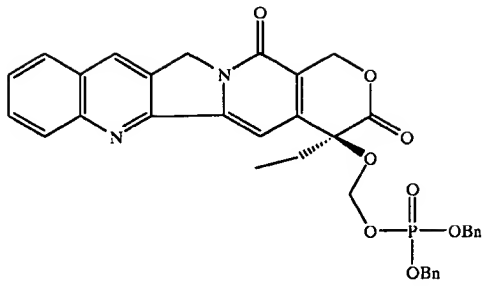

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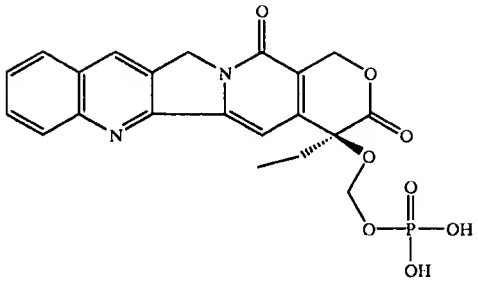


To a well stirred suspension of 20-O-methylthiomethylcamptothecin (1.00 g, 2.44 mmol) and powdered, activated 4 Å molecular sieves (5 g) in tetrahydrofuran (20 mL) was added a suspension of N-iodosuccinimide (2.00 g of 95%, 8.44 mmol) and dibenzylphosphate (2.20 g, 7.83 mmol) in methylene chloride (12 mL). The resulting mixture was vigorously stirred at room temperature for 30 minutes, filtered, and diluted with ethyl acetate (300 mL). The solution was washed with aqueous sodium thiosulfate (10%, 2×15 mL), water (2×20 mL), brine (50 mL), and dried over magnesium sulfate. The mixture was filtered and the solvent was evaporated under reduced pressure. The brown oily residue was purified by silica gel flash column chromatography (98:2 ethyl acetate/methanol) and dried in vacuo overnight to give 1.19 g (76% yield) of the title compound as a yellow foam. α^{D}_{20}-43.1° (c 0.55, $CHCl_3$).

FABMS+(NBA): $[MH]^+$, m/z 639.

^1H NMR (400 MHz, $CDCl_3$, δ): 0.91 (t, J=7.4 Hz, 3H), 2.09 (sext, J=7.4 Hz, 1H), 2.26 (sext, J=7.4 Hz, 1H), 5.06 (m, 4H), 5.28 (m, 3H), 5.35 (d, J=17.0 Hz, 1H), 5.48 (2xd, J=10.5 Hz, 1H), 5.64 (d, J=17.3 Hz, 1H), 7.59 (s, 1H), 7.67 (t, J=7.0 Hz, 1H), 7.80 (t, J=7.1 Hz, 1H), 7.94 (d, J=8.0 Hz, 1H), 8.13 (d, =8.5 Hz, 1H), 8.35 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 7.73, 29.53, 32.49, 49.86, 66.74, 69.37, 69.44, 78.48, 88.99, 89.04, 98.09, 121.55, 127.65, 127.70, 127.90, 128.01, 128.25, 128.35, 128.36, 129.62, 130.48, 130.97, 135.45, 135.55, 145.47, 145.82, 148.76, 152.15, 157.18, 168.67.

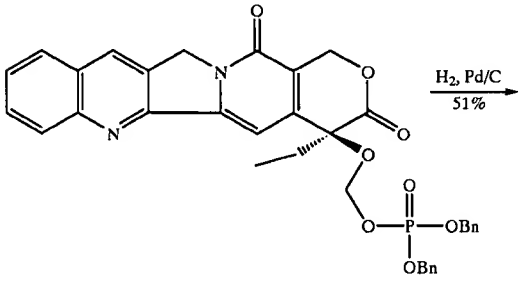
To a solution of 20-O-phosphonooxymethylcamptothecin dibenzyl ester (500 mg, 0.78 mmol) in tetrahydrofuran (100 mL) and water (5 mL) was added palladium on carbon (10%, 500 mg). This mixture was stirred under an atmosphere of hydrogen (1 atm) for 35 minutes. The catalyst was removed by filtration through Celite. The Celite was then washed with tetrahydrofuran (300 mL) and the combined filtrates were evaporated at reduced pressure. The resulting green solid was washed with ether (2×20 mL), hexane (50 mL), dried in vacuo, and then dissolved in hot methanol (60 mL). The solution was filtered, concentrated at reduced pressure to ~10 mL volume. After standing at room temperature for one hour, the solution was placed in the refrigerator overnight. The crystalline precipitate that had formed overnight was filtered off and dried in vacuo to give 155 mg of the title compound as a yellow solid. The filtrate was concentrated to ~1 mL volume and kept in A the refrigerator for one hour to give an additional 28 mg of the product. Total yield: 183 mg (51%).

FABMS+(NBA): $[MH]^+$, m/z 459, $[M+Na]^+$, m/z 481.

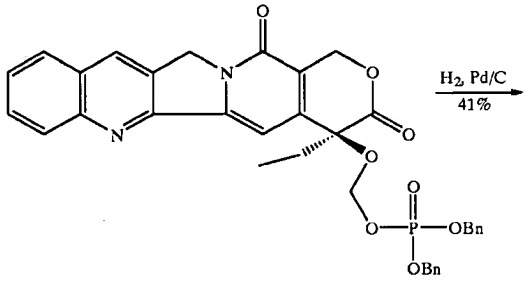
^1H NMR (400 MHz, D_2O, δ): 0.95 (t, J 7.5 Hz, 3H), 2.25 (m, 2H), 4.98 (d, J=5.0 Hz, 2H), 5.14 (2xd, J=9.3 Hz, 1H), 5.22 (2xd, J=8.9 Hz, 1H), 5.48 (d, J=17.0 Hz, 1H), 5.60 (d, J=16.9 Hz, 1H), 7.54 (s, 1H), 7.56 (t, J=7.7 Hz, 1H), 7.77 (t, J=7.2 Hz, 1H), 7.86 (d, J=8.2 Hz, 1H), 8.01 (d, J=8.5 Hz, 1H), 8.44 (s, 1H).

Chemical structure and purity of the product were also confirmed by ^1H NMR spectroscopy of its disodium salt, formed from the acid and two mole equivalents of sodium bicarbonate in D_2O.

IIIc. Synthesis of 20-O-phosphonooxymethylcamptothecin:



IIIc. Synthesis of 20-O-phosphonooxymethylcamptothecin (alternate run):



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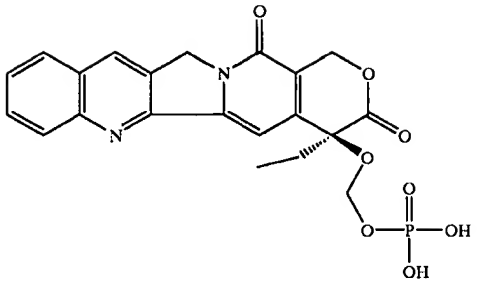
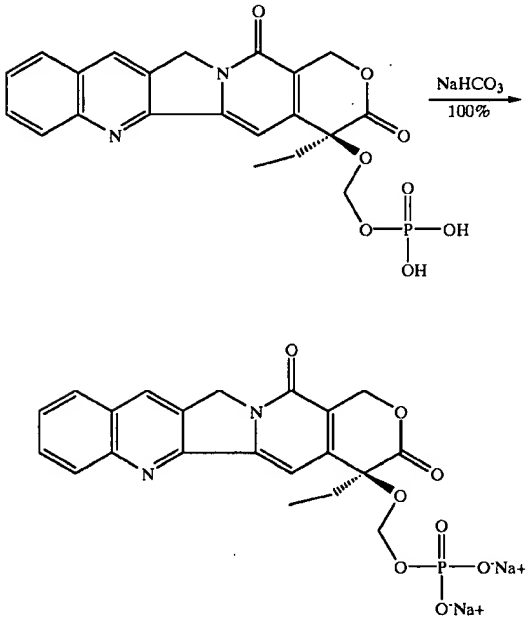


To a solution of 20-O-phosphonooxymethylcamptothecin dibenzyl ester (500 mg, 0.78 mmol) in tetrahydrofuran (100 mL) and water (5 mL) was added palladium on carbon (10%, 500 mg). The mixture was stirred under an atmosphere of hydrogen (1 atm) for 30 minutes. The catalyst was removed by filtration through Celite. Celite was washed with tetrahydrofuran (2×100 mL), and the combined filtrates were treated with an aqueous solution of sodium carbonate hydrate (97 mg in 2 mL water, 0.78 mmol). THF was evaporated at reduced pressure and the heterogeneous aqueous residue was diluted with water (10 mL) and extracted with ethyl acetate (2×3 mL). The resulting yellow homogeneous solution was acidified with hydrochloric acid (10%) to pH=1. The resulting precipitate was filtered off and dried in vacuo overnight to give 145 mg (41% yield) of the title compound as a yellow solid.

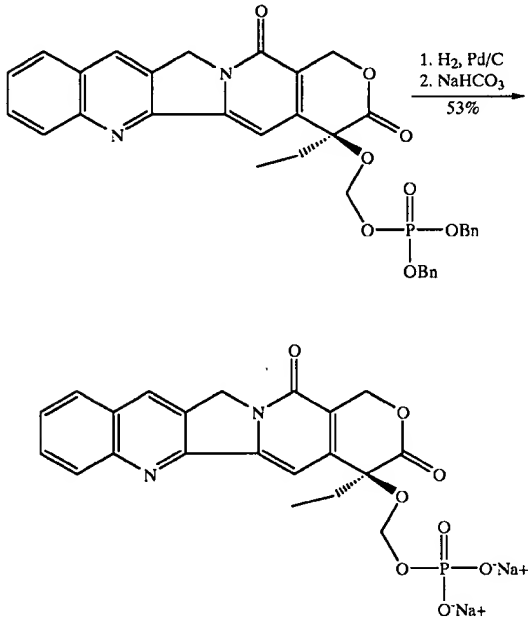
IIId. Synthesis of 20-O-phosphonooxymethylcamptothecin disodium salt:



To a suspension of 20-O-phosphonooxymethylcamptothecin (5 mg, 10.9 μmol) in deuterium oxide (0.5 mL) was added a deuterium oxide solution of sodium bicarbonate (50 μl of 0.44M solution=22 μmol). The heterogeneous mixture was sonicated for a few minutes to give a yellow homogenous solution of the title product.

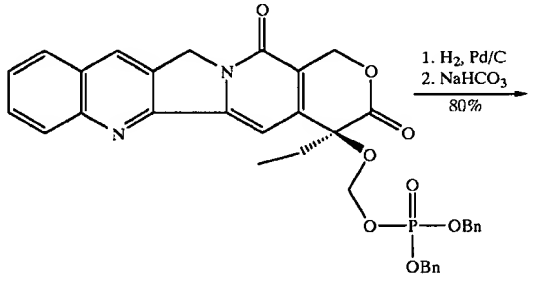
^{1}H NMR (400 MHz, D_2O, after 10 min., 96% lactone, 4% carboxylate, δ): 1.05 (t, J=7.2 Hz, 3H), 2.27 (m, 2H), 4.57 (d, J=18.8 Hz, 1H), 4.70 (d, J=18.9 Hz, 1H), 5.06 (dd, J=8.3, J=5.4 Hz, 1H), 5.18 (dd, J=7.6, J=5.5 Hz, 1H), 5.45 (d, J=16.7 Hz, 1H), 5.59 (d, J=16.8 Hz, 1H), 7.34 (t, J=7.1 Hz, 1H), 7.41 (s, 1H), 7.60 (m, 2H), 7.81 (d, J=8.3 Hz, 1H), 8.17 (s, 1H).

IIId. Synthesis of 20-O-phosphonooxymethylcamptothecin disodium salt (alternate run 1):



To a solution of 20-O-phosphonooxymethylcamptothecin dibenzyl ester (78 mg, 0.122 mmol) in tetrahydrofuran (10 mL) and water (3 mL) was added palladium on carbon (10%, 80 mg). The mixture was stirred under an atmosphere of hydrogen (1 atm) for 30 minutes. The catalyst was removed by filtration through Celite and the filtrate was treated with an aqueous solution of sodium bicarbonate (20 mg in 0.5 mL of water, 0.238 mmol). The yellow precipitate was filtered off, washed with methylene chloride, and dried in vacuo to give 35 mg (57% yield) of the title compound (light brown solid) as a mixture of its lactone form (82%) and its carboxylate form (18%) (by ^{1}H NMR).

IIId. Synthesis of 20-O-phosphonooxymethylcamptothecin disodium salt (alternate run 2):



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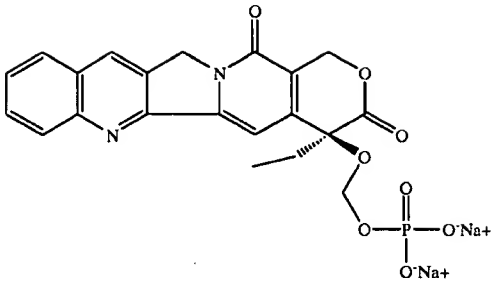
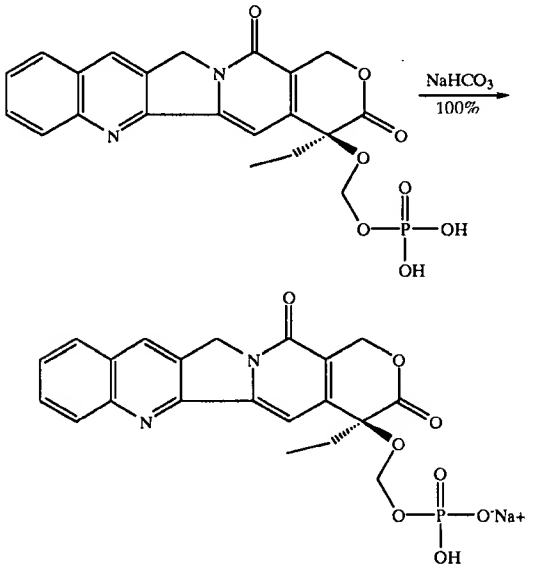


To a solution of 20-O-phosphonooxymethylcamptothecin dibenzyl ester (500 mg, 0.78 mmol) in tetrahydrofuran (100 mL) and water (5 mL) was added palladium on carbon (10%, 500 mg). This mixture was stirred under an atmosphere of hydrogen (1 atm) for 30 minutes. The catalyst was removed by filtration through Celite. Celite was washed with tetrahydrofuran (50 mL), and the combined filtrates were treated with an aqueous solution of sodium carbonate hydrate (90 mg in 2 mL of water, 0.72 mmol). Tetrahydrofuran was evaporated at reduced pressure, and the residue was dissolved in water (15 mL). The heterogeneous mixture was extracted with ethyl acetate (2×15 mL) and ether (20 mL) and the resulting aqueous homogenous solution was evaporated to dryness under a stream of argon at room temperature. The residue was dried in vacuo overnight to give 290 mg (80% yield) of the title compound (orange solid) as a mixture of its lactone form (60%), its carboxylate form (40%), and a small amount of byproducts (by ^{1}H NMR).

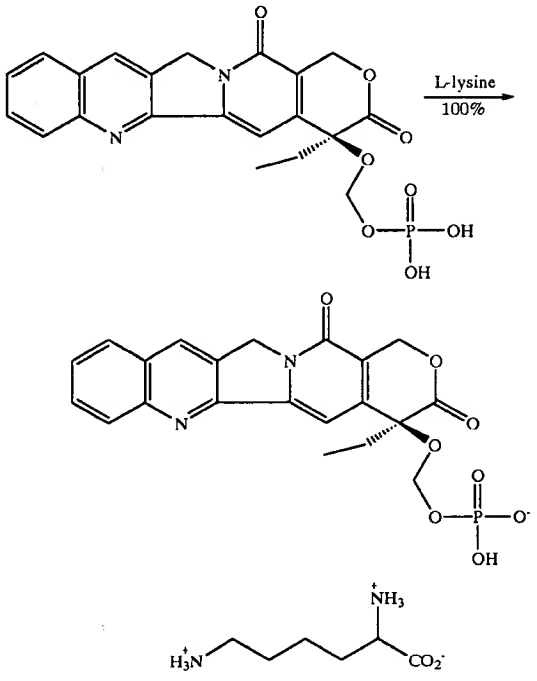
IIIe. Synthesis of 20-O-phosphonooxymethylcamptothecin monosodium salt:



To a continuously sonicated suspension of 20-O-phosphonooxymethylcamptothecin (5 mg, 10 μmol) in deuterium oxide (0.5 mL) was added dropwise a deuterium oxide solution of sodium bicarbonate until complete homogenization was achieved (21 μl of 0.44M solution=9.2 μmol). A yellow homogenous solution of the title compound was obtained.

^{1}H NMR (400 MHz, D_2O, δ): 1.00 (t, J=7.2 Hz, 3H), 2.23 (m, 2H), 4.40 (d, J=18.8 Hz, 1H), 4.50 (d, J=18.8 Hz, 1H), 5.10 (dd, J=9.7, J=5.9 Hz, 1H), 5.26 (dd, J=9.0, J=6.1 Hz, 1H), 5.39 (d, J=16.7 Hz, 1H), 5.50 (d, J=16.7 Hz, 1H), 7.20 (t, J=7.3 Hz, 1H), 7.28 (s, 1H), 7.46 (m, 2H), 7.66 (d, J=8.4 Hz, 1H), 8.02 (s, 1H).

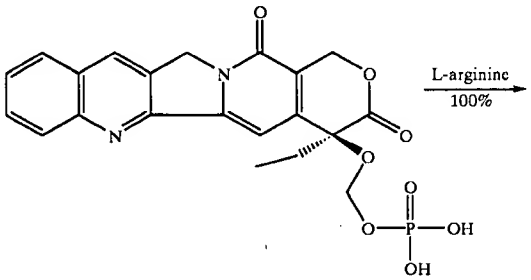
IIIf. Synthesis of 20-O-phosphonooxymethylcamptothecin lysine salt:



To a continuously sonicated suspension of 20-O-phosphonooxymethylcamptothecin (5 mg, 10 μmol) in deuterium oxide (0.5 mL) was added dropwise a deuterium oxide solution of L-lysine (25 μl of 0.43M solution=10.7 μmol) until complete homogenization was achieved. A yellow homogenous solution of the title compound was obtained.

^{1}H NMR (400 MHz, D_2O, 94% lactone, 6% carboxylate, δ): 1.02 (t, J=7.2 Hz, 1H), 1.49 (m, 2H), 1.73 (m, 2H), 1.88 (m, 2H), 2.25 (m, 2H), 3.03 (t, J=7.5 Hz, 2H), 3.76 (t, J=6.0 Hz, 1H), 4.43 (d, J=19.0 Hz, 1H), 4.52 (d, J=18.9 Hz, 1H), 5.11 (dd, J=9.7, J=5.8 Hz, 1H), 5.27 (dd, J=9.2, J=5.8 Hz, 1 H), 5.41 (d, J=16.7 Hz, 1 H), 5.53 (d, J=16.7 Hz, 1H), 7.23 (t, J=7.4 Hz, 1H), 7.30 (s, 1H), 7.49 (m, 2H), 7.68 (d, J=8.4 Hz, 1H), 7.04 (s, 1H) .

IIIg. Synthesis of 20-O-phosphonooxymethylcamptothecin arginine salt:



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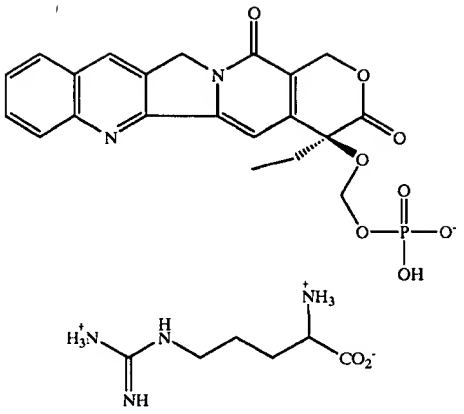
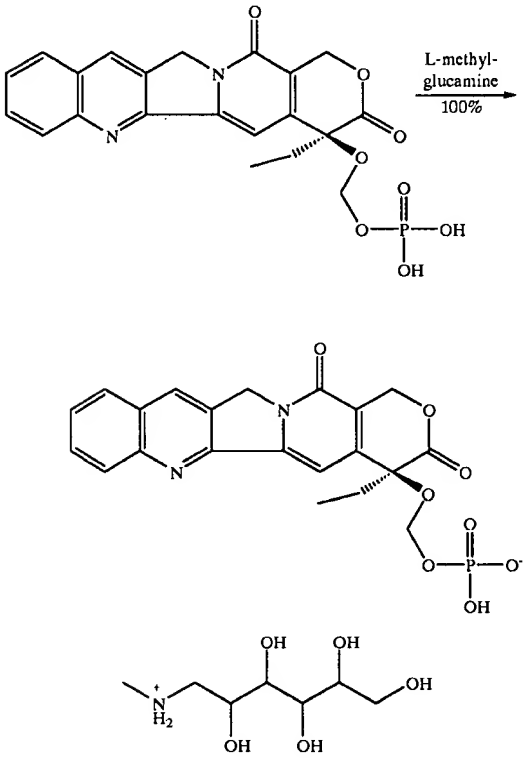


To a continuously sonicated suspension of 20-O-phosphonooxymethylcamptothecin (5 mg, 10 μmol) in deuterium oxide (0.5 mL) was added dropwise a deuterium oxide solution of L-arginine (27 μl of 0.40M, 10.8 μmol) until complete homogenization was achieved. A yellow homogenous solution of the title compound was obtained.

^{1}H NMR (400 MHz, D_2O, δ): 1.02 (t, J=7.1 Hz, 1H), 1.66 (m. 2), 1.89 (m, 2H), 2.25 (m, 2H), 3.20 (t, J=6.8 Hz, 2H), 3.77 (t, J=6.0 Hz, 1H), 4.40 (d, J=19.0 Hz, 1H), 4.49 (d, J=18.8 Hz, 1H), 5.12 (dd, J=9.7, J=6.0 Hz, 1H), 5.29 (dd, J=8.8, J=6.1 Hz, 1H), 5.40 (d, J=16.7 Hz, 1H), 5.51 (d, J=16, 7 Hz, 1H), 7.20 (t, J=7.3 Hz, 1H), 7.29 (s, 1H), 7.47 (m, 2H), 7.66 (d, J=8.3 Hz, 1H), 8.03 (s, 1H).

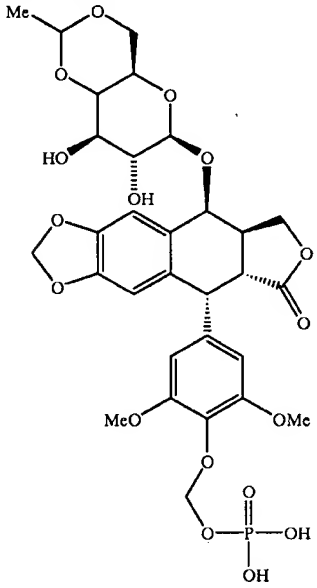
IIIh. Synthesis of 20-O-phosphonooxymethylcamptothecin N-methylglucamine salt:



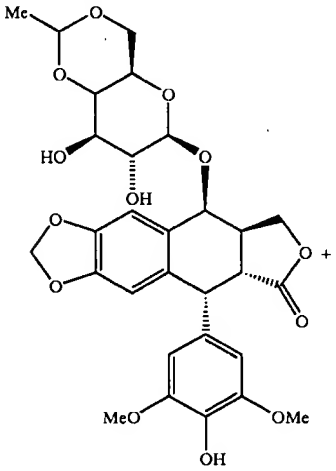
To a continuously sonicated suspension of 20-O-phosphonooxymethylcamptothecin (5 mg, 10.9 μmol) in deuterium oxide (0.5 mL) was added dropwise a deuterium oxide solution of (D)-N-methylglucamine (21 μl of 0.51M solution=10.7 μmol) until complete homogenization was achieved. A yellow homogenous solution of the title compound was obtained.

^{1}H NMR (400 MHz, D_2O, δ): 1.02 (t, J=7.3 Hz, 3H), 2.25 (m, 2H), 2.78 (s, 3H), 3.20 (m, 2H), 3.65 (m, 2H), 3.80 (m, 3H), 4.11 (m, 1H), 4.44 (d, J=18.9 Hz, 1H), 4.53 (d, J=19.0 Hz, 1H), 5.12 (dd, J=9.8, J=5.9 Hz, 1H), 5.27 (dd, J=9.2, J=5.9 Hz, 1H), 5.41 (d, J=16.7 Hz, 1H), 5.53 (d, J=16.7 Hz, 1H), 7.23 (t, J=7.4 Hz, 1H), 7.49 (m, 2H), 7.69 (d, J=8.4 Hz, 1H), 8.05 (s, 1H).

IV. Synthesis of 4'-0-phosphonoocymethyletoposide:



IVa. Synthesis of 4'-0-phosphonoocymethyletoposide dibenzyl ester:



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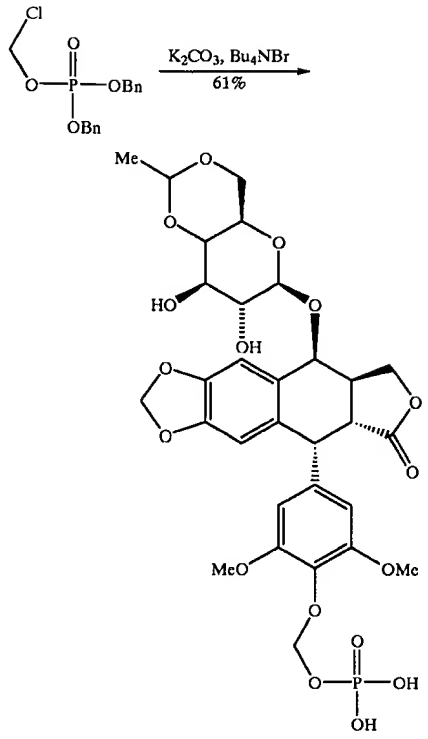


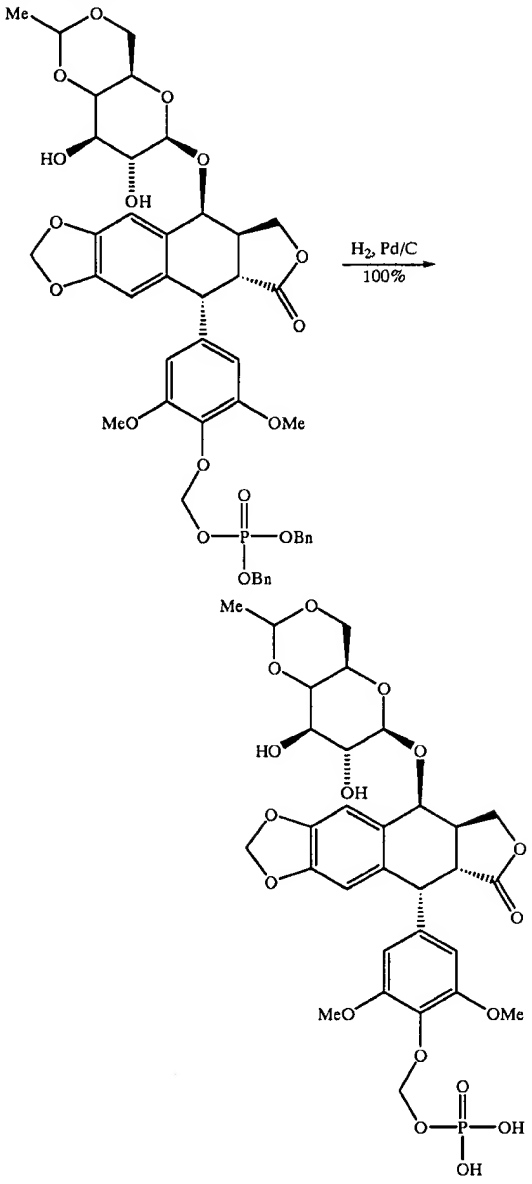
To a solution of chloromethyl dibenzylphosphate (670 mg, 2.05 mmol), etoposide (300 mg, 0.51 mmol), and tetrabutylammonium bromide (164.4 mg, 0.51 mmol) in tetrahydrofuran (0.5 mL) was added powdered potassium carbonate (352.4 mg, 2.55 mmol). The resulting reaction mixture was vigorously stirred at room temperature for 35 minutes. The mixture was then directly purified by silica gel flash column chromatography (30:1 methylene chloride/methanol) to give 272 mg (61% yield) of the title compound as a white solid with more than 95% of the trans stereochemistry retained.

FABMS+(NBA): $[MH]^+$, m/z 879.

^1H NMR (400 MHz, $CDCl_3$, δ): 1.41 (d, J=5.0 Hz, 3H), 2.79 (br, s, 1H), 2.86 (m, 1H), 2.97 (br s, 1H), 3.30 (dd, J=14.2, J=5.3 Hz, 1H), 3.35 (m, 2H), 3.45 (t, J=8.5, J=8.0 Hz, 1H), 3.59 (m, 1H), 3.66 (s, 6H), 3.74 (m, 1H), 4.19 (m, 1H), 4.20 (t, J=8.5, J=8.0 Hz, 1H), 4.42 (dd, J=10.3, J=9.1 Hz, 1H), 4.60 (d, J=5.2 Hz, 1H),4.64(d, J=7.6Hz, 1H), 4.76 (q, J=5.0 Hz, 1H), 4.92 (d, J=3.4 Hz, 1H), 5.03 (dd, J=7.3, J=4.3 Hz, 4H), 5.54 (dd, J=11.7, J=5.1 Hz, 1H), 5.59 (dd, J=11.3, J=5.1 Hz, 1H), 5.99 (d, J=3.5 Hz, 2H), 6.26 (s, 2H), 6.51 (s, 1H), 6.84 (s, 1H), 7.33 (m, 10H).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 20.21, 37.49, 41.00, 43.78, 56.07, 66.32, 67.87, 67.97, 69.06, 69.14, 73.01, 73.29, 74.47, 79.70, 92.55, 92.62, 99.70, 101.57, 101.72, 107.89, 109.13, 110.55, 127.82, 127.97, 128.15, 128.35, 128.43, 132.40, 133.08, 135.68, 135.78, 136.49, 147.14, 148.73, 152.18, 174.90.

IVb. Synthesis of 4'-O-phosphonoocymethyletoposide:



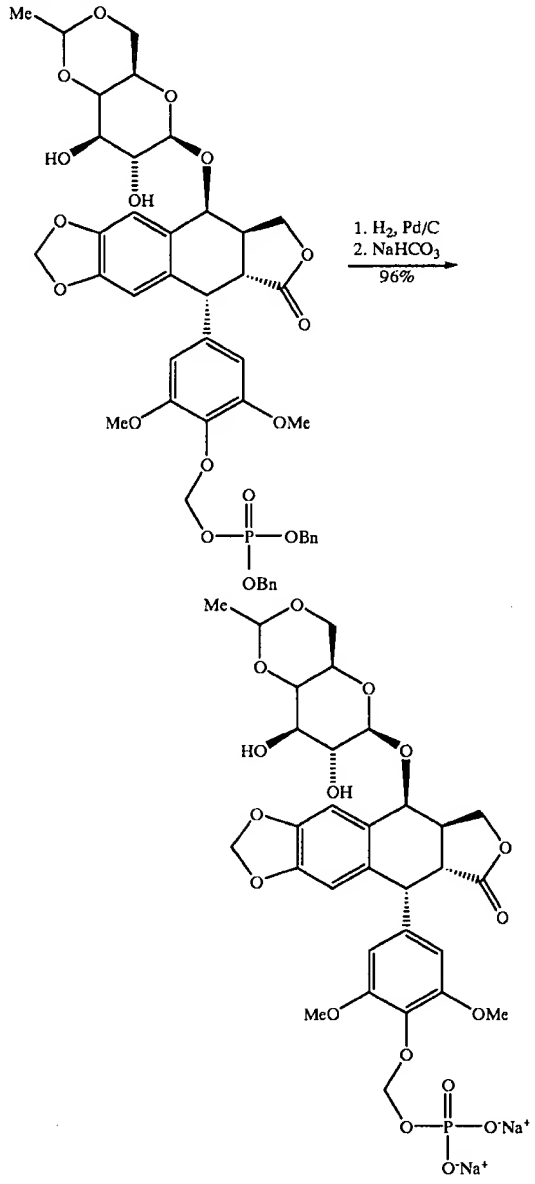
To a solution of 4'-O-phosphonooxymethyletoposide dibenzyl ester (20.5 mg, 0.023 mmol) in tetrahydrofuran (2 mL) was added palladium on carbon (10%, 5 mg). The mixture was stirred under an atmosphere of hydrogen (1 atm) for 10 minutes. The catalyst was removed by filtration through Celite, and tetrahydrofuran was evaporated at reduced pressure. The resulting residue was dried in vacuo to give 16 mg (100% yield) of the title compound as a white solid.

FABMS+(NBA): $[MH]^+$, m/z 699.

^1H NMR (400 MHz, $CDCl_3$/ DMSO-d_6, δ): 1.29 (d, J=5.0 Hz, 3H), 2.78 (m, 1H), 3.21 (m, 2H), 3.29 (t, J=8.6, J=7.8 Hz, 1H), 3.37 (dd, J=14.0, J=5.3 Hz, 1H), 3.52 (m, 2H), 3.62 (s, 6H), 4.09 (m, 1H), 4.17 (t, J=8.1 Hz, 1H), 4.38 (dd, J=8.8,

J=8.7 Hz, 1H), 4.44 (d, J=7.6 Hz, 1H), 4.48 (d, J=5.3 Hz, 1H), 4.66 (q, J=5.0 Hz, 1H), 4.88 (d, J=3.3 Hz, 1H), 5.05 (br s, 7H), 5.40 (dd, J=10.7, J=7.8 Hz, 1H), 5.43 (dd, J=10.4, J=7.5 Hz, 1H), 5.89 (dd, J=8.8 Hz, 1H), 6.18 (s, 2H), 6.41 (s, 1H), 6.78 (s, 1H).

IVc. Synthesis of 4'-0-phosphonoocymethyletoposide disodium salt:



To a solution of 4'-O-phosphonooxymethyletoposide dibenzyl ester (200 mg, 0.227 mmol) in tetrahydrofuran (10 mL) was added palladium on carbon (10%, 45 mg). This mixture was stirred under an atmosphere of hydrogen (1 atm) for 25 minutes. The catalyst was removed by filtration through Celite. The filtrate was evaporated at reduced pressure, and the residue was dried in vacuo. The resulting white solid was dissolved in an aqueous solution of sodium bicarbonate. (2.9 mL of 0.136M=0.394 mmol). The resulting heterogeneous mixture was mixed with activated carbon, stirred for a few minutes, and was then filtered through a 40 μm filter unit. The homogenous, colorless filtrate was lyophilized to give 140 mg (96% yield) of the title compound as a white solid with more than 95% of bans stereochemistry retained.

FABMS+(NBA): $[MH]^+$, m/z 743, $[M-Na+2H]^+$, m/z 721, $[M-2Na+3H]^+$, m/z 699.

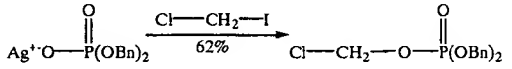
^1H NMR (400 MHz, D_2O, δ): 1.37 (d, J=5.1 Hz, 3H), 3.10 (m, 1H), 3.37 (dd, J=8.9, J=8.0 Hz, 1H), 3.48 (m, 2H), 3.65 (m, 3H), 3.75 (s, 6H), 4.29 (dd, J=10.4, J=4.5 Hz, 1H), 4.41 (t, J=8.3, J=8.0 Hz, 1H), 4.49 (dd, J=10.5, J=8.9 Hz, 1H), 4.68 (d, J=5.7 Hz, 1H), 4.74 (d, J=7.8 Hz, 1H), 4.91 (q, J=5.0 Hz, 1H), 5.13 (d, J=3.0 Hz, 1H), 5.26 (2xd, J=5.3, J=3.3 Hz, 1H), 5.28 (2xd, J=5.3, J=3.3 Hz, 1H), 5.98 (d, J=10.5 Hz, 2H), 6.40 (s, 2H), 6.58 (s, 1H), 7.00 (s, 1H).

^3C NMR (125 MHz, D_2O, δ): 22.13, 40.74, 43.56, 46.11, 59.12, 68.70, 70.41, 72.40, 75.46, 75.95, 76.95, 82.46, 94.87, 102.88, 103.66, 104.62, 111.14, 112.82, 113.23, 130.73, 135.45, 135.74, 140.22, 149.56, 151.43, 154.94, 166.36, 181.61.

^{31}P NMR (200 MHz, D20, δ): s (2.19).

V. Synthesis of Phosphonooxymethylating Agents

Va. Synthesis of chloromethyldibenzyl phosphate



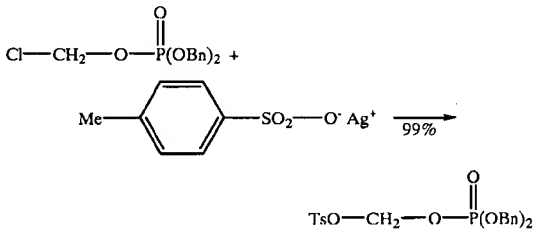
To a refluxed solution of chloroiodomethane (25 g of 97%, 0.14 mol) in toluene (HPLC-grade, 30 mL) was added silver dibenzylphosphate (7.0 g, 0.018 mol) in several portions over 20 minutes. Refluxing was continued for one hour. After the reaction mixture was cooled down to room temperature and filtered, the solvent was evaporated under reduced pressure. The oily residue was purified by silica gel flash column chromatography (7:3 hexane/ethyl acetate) to give 3.63 g (62% yield) of the title compound as a yellow oil.

FABMS+(NBA): $[MH]^+$, m/z 327

^1H NMR (300 MHz, $CDCl_3$, δ): 5.10 (d, J=8.0 Hz, 4H), 5.63 (d, J=15.7 Hz, 2H), 7.36 (s, 10H).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 69.68, 69.75, 73.33, 73.42, 127.93, 128.51, 128.63, 135.07.

Vb. Synthesis of dibenzyl (p-toluenesulfonemethyl)-phosphate:

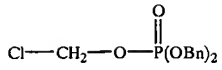


To a stirred solution of silver p-toluenesulfonate (600 mg, 2.15 mmol) in dry acetonitrile (3 mL) was added chloromethyl dibenzylphosphate (150 mg, 0.46 mmol) under an argon atmosphere. After the reaction mixture was stirred for 21 hours at room temperature, the solvent was removed, and the residue extracted with ether (3×3 mL) . The combined extracts were filtered, evaporated, and dried in vacuo to give 210 mg (99% yield) of the title compound as a white solid.

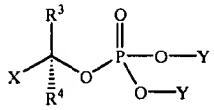
EIMS: $[MH]^+$, m/z 463.

^1H NMR (300 MHz, $CDCl_3$, δ): 2.37 (s, 3H), 4.91 (2 xd, J=7.9 Hz, 4H), 5.61 (d, J=14.2 Hz, 2H), 7.29 (m, 12H), 7.78 (d, J=8.4 Hz, 2H).

With respect to the above reaction Vb, as explained also in Ic above, the reagent:

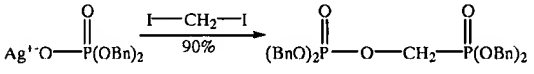


can be generically represented by the following formula:



wherein all symbols are the same as defined above.

Vc. Synthesis of formaldehyde bis(dibenzyloxyphosphono)-acetal:



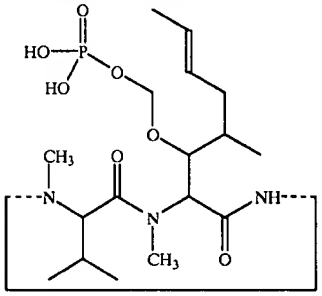
To a solution of diiodomethane (4 mL, 50 mmol) in dry toluene (15 mL) was added silver dibenzylphosphate (3.0 g, 7.8 mmol). The resulting mixture was refluxed for 15 minutes under an argon atmosphere. The mixture was then cooled down to room temperature and filtered. Then the solvent was evaporated in vacuo. The oily residue was purified by silica gel flash column chromatography (1:1 hexane/ethyl acetate and then ethyl acetate) to yield a yellowish oil which then crystallized to give 1.97 g (90% yield) of the title compound as a white solid, mp 39–42° C.

CIMS (NH3): $[MH]^+$, m/z 569.

^1H NMR (300 MHz, CDC_3, δ): 5.03 (d, J=7.9 Hz, 8H),5.49 (t, J=14.3 Hz, 2H), 7.30 (m, 20H).

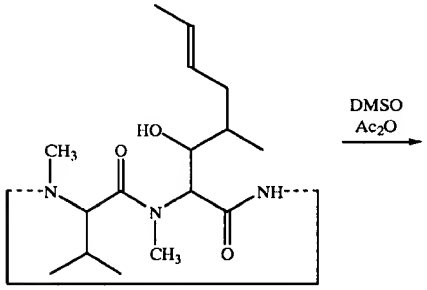
^{13}C NMR (75 MHz, $CDCl_3$, δ): 69.54, 69.61, 86.48, 127.88, 128.48, 128.55, 135.10, 135.20.

VI - Synthesis of O-Phosphonooxymethylcyclosporin A:



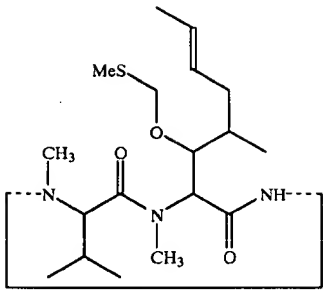
Cyclosporin A

VIa. Synthesis of O-methylthiomethylcyclosporin A:



Cyclosporin A

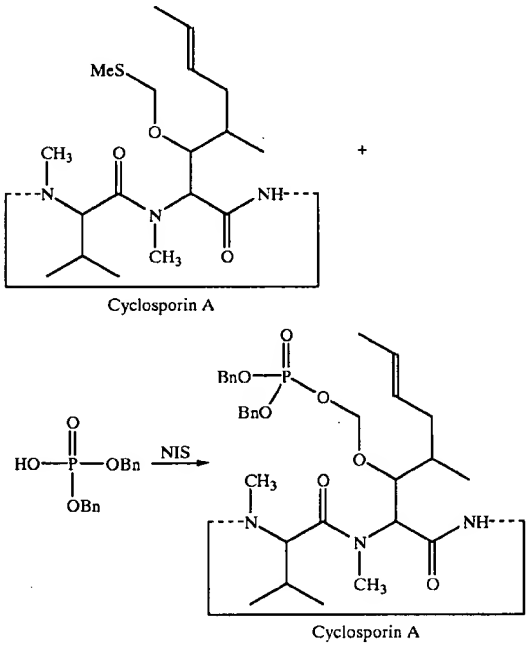
-continued



Cyclosporin A

To a suspension of Cyclosporin A in dimethylsulfoxide (250 mL) is added acetic anhydride (125 mL) and acetic acid (35 mL). The heterogeneous mixture is vigorously stirred at room temperature for 24 hours, poured into ice (800 mL), stirred for 30 minutes, and then extracted with methylene chloride (4×100 mL). The combined methylene chloride extracts are washed with water (2×100 mL) and dried over magnesium sulfate. The methylene chloride is removed at reduced pressure to provide a product. The product is further purified by silica gel chromatography.

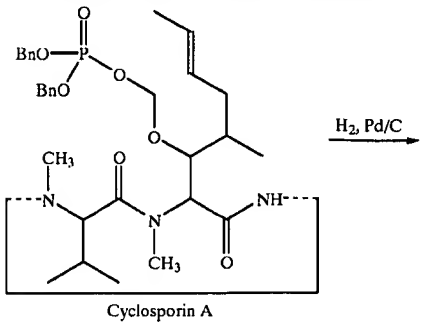
VIb. Synthesis of O-phosphonooxymethylcyclosporin A dibenzyl ester:



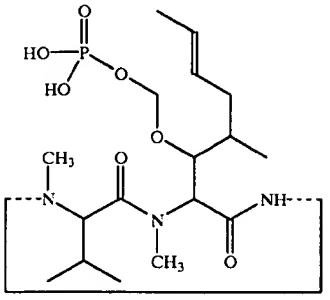
Cyclosporin A

To a well stirred suspension of O-methylthiomethylcyclosporin A and powdered, activated 4 Å molecular sieves (5 g) in tetrahydrofuran (20 mL) is added a suspension of N-iodosuccinimide (2.00 g of 95%, 8.44 mmol) and dibenzylphosphate (2.20 g, 7.83 mmol) in methylene chloride (12 mL). The resulting mixture is vigorously stirred at room temperature for 30 minutes, filtered, and diluted with ethyl acetate (300 mL). The solution is washed with aqueous sodium thiosulfate (10%, 2×15 mL), water (2×20 mL), brine (50 mL), and dried over magnesium sulfate. The mixture is filtered and the solvent is evaporated under reduced pressure. The residue is purified by silica gel flash column chromatography.

VIc. Synthesis of O-phosphonooxymethylcyclosporin A:



Cyclosporin A



Cyclosporin A

To a solution of O-phosphonooxymethylcyclosporin A dibenzyl ester in tetrahydrofuran (100 mL) and water (5 mL) is added palladium on carbon (10%, 500 mg). This mixture is stirred under an atmosphere of hydrogen (1 atm) for 35 minutes. The catalyst is removed by filtration through Celite. The Celite is then washed with tetrahydrofuran (300 mL) and the combined filtrates are evaporated at reduced pressure. The resulting solid is washed with ether (2x20 mL), hexane (50 mL), dried in vacuo, and then dissolved in hot methanol (60 mL). The solution is filtered, concentrated at reduced pressure to ~10 mL volume. After standing at room temperature for one hour, the solution is placed in a refrigerator overnight. The crystalline precipitate that forms overnight is filtered off and dried in vacuo to give the title compound as a solid. The filtrate is concentrated to ~1 mL volume and kept in the refrigerator for one hour to give additional product.

BIOLOGICAL EVALUATION

Compounds of the present invention are novel pharmaceutical agents; representative compounds of formula I have been evaluated in in vitro and in vivo conversion studies. In all of these studies the prodrugs were converted into their pharmaceutically active parent compounds.

(1) Solubility Estimate of Propofol Prodrug in Water

The water solubility of propofol prodrug is approximately 500 mg/mL based on HPLC analysis of saturated aqueous solution.

(2) in vitro conversion of propofol prodrug to propofol

The in vitro conversion of propofol prodrug to propofol was performed using alkaline phosphatase in glycine buffer pH 10.4 medium. 25 mL of a 100 μg/mL propofol prodrug solution in glycine buffer was prepared. One millimeter was saved for a zero time point and the remaining 24 mL were placed in a 37° C. water bath. 960 μL of a 0.1 mg/mL alkaline phosphatase in glycine buffer solution was added to the 24 mL of propofol prodrug solution, mixed, and returned to the water bath. 1.5 mL samples were removed at 5, 10, 20, 30, 40, 60, 90, 120, 180, 240, 300, and 360 minutes. To each sample, 10 μL of glacial acetic acid was added immediately to stop the enzymatic reaction. The samples were assayed by HPLC to quantitate the propofol prodrug and propofol concentration. The results of the in vitro conversion are shown in FIG. 1. These results demonstrate that the propofol prodrug is a substrate for alkaline phosphatase.

(3) Gross Toxicity Evaluation in Rats

Propofol prodrug was prepared for i.v. injection at a concentration of 68 mg/mL in 0.9% Sodium Chloride Injection, USP. This concentration is equivalent to 36 mg/mL of propofol. The propofol prodrug solution was filtered through a 0.22 μm nylon membrane prior to administration.

The evaluation of the propofol prodrug on rats was conducted with two male Harlen Sprague-Dawley rats weighing 820 and 650 g. The 820 g rat received 200 μL of the propofol prodrug i.v. formulation (equivalent to 9 mg/kg of propofol) in the tail vein. A blood sample was taken from the tail vein (with heparinized syringe) after approximately 12 minutes. The 650 g rat received a dose of the mild sedative Metaphane® prior to receiving the propofol prodrug formulation. The 650 g rat was injected with 125 μL of the propofol prodrug formulation in the tail vein and a blood sample was taken from the tail vein (with heparinized syringe) after approximately six minutes. The blood samples from both rats were assayed for propofol by HPLC.

The results of the propofol prodrug injection in both rats were similar. Both rats became unsteady after a few minutes, but never lost their righting reflex. Based on visual observations, the rats fully recovered from the propofol prodrug injections. Blood removed from both rats confirmed the presence of propofol through HPLC analysis. The rats did not display signs of discomfort due to the propofol prodrug.

(4) Pharmacokinetic Evaluation in Dogs

A pharmacokinetic study involving Diprivan® or the propofol prodrug was performed in a dog with a sufficient washout period between studies. The blood concentrations were determined using HPLC with fluorescence detection while brain activity was monitored with two lead electroencephalography (EEG). Prior to dosing the dog, the dog was blindfolded, cotton was placed in the ears of the dog, and the legs of the dog were bound to minimize movement and other outside stimuli so that the effect of the propofol on the dog's brain wave activity could be most efficiently monitored.

The evaluation of the propofol blood concentration versus time was conducted with a beagle weighing ~13 kg. Approximately 8 mL of blood was taken prior to injection to be used for standard curve preparation and a zero time blood level. The dog received a volume of Diprivan® or propofol prodrug formulation equivalent to 7 mg/kg of propofol via injection in the cephalic vein.

Two mL blood samples were taken from either the cephalic (not the same vein as the formulation injection site), jugular, or saphenous vein (with heparinized syringe) after 1, 3, 5, 10, 15, 20 and 30 minutes after the injection. Blood samples were also taken after 60, 90, 120, 180, 240, 300, 360, 480, and 1440 minutes. Blood samples were extracted to remove the propofol immediately after being taken from the dog. The dog was fasted for approximately 20 hours prior to receiving the Diprivan® or propofol prodrug formulation. After the 120 minute sample was taken, the dog was allowed to drink water. Food was given to the dog after the 480 minute blood sample was obtained. The dog's regular diet was Hills' Science Diet Maintenance. The dog was on a light/dark cycle of 12 hours of light per day.

The concentration of propofol in the blood samples was determined using HPLC with fluorescence detection. The results are shown in FIG. 2. The blood extraction and HPLC methods used were based on work reported by Plummer (1987) with minor modifications. The sample preparation and assay procedure used were as follows:

To a 1 mL sample of blood, 10 μL of thymol internal standard (20 μg/mL) and 1 mL phosphate buffer (0.1M, pH 7.2) were added, vortexing to mix after each addition. Five mL of cyclohexane was then added and the samples were mixed at 75 rpm for 20–30 minutes. The organic layer was separated by 1 minute of centrifugation at approximately 2000 rmp. Approximately 4.5 mL of the organic layer was transferred to a tube containing 50 μL of dilute tetramethylammonium hydroxide (TMAH) solution at approximately 1.8% (w/v). The solvent was evaporated to dryness under a stream of nitrogen and reconstituted with 200 μL of Mobile Phase A. The samples were centrifuged at 15,000 rmp for 30 seconds to remove any particles, and the supernatant was injected on the HPLC. Standard curve samples were prepared by spiking 1 mL aliquots of the initial blood with propofol at concentrations 5, 1, 0.5, 0.1 and 0.01 μg/mL. These standards were treated the same as the samples.

The HPLC system consisted of the following Shimadzu components: LC-10AT pumps, SCL-10A system controller, RF 353 fluorescence detector, and SIL-10A auto sampler. The HPLC parameters were as follows: excitation at 275 nm and emission at 320 nm; flow rate at I mL/min; injection volume was 3–30 μL depending on propofol concentration. The HPLC column was a Zorbax RX-C18, 15 cm×4.6 mm i.d., 5 μm particle size. Mobile Phase A was 60:40 (v/v) acetonitrile: 25 mM phosphate, 15 mM TBAP Buffer pH 7.1. Mobile Phase B was 80:10:10 (v/v/v) acetonitrile: water: THF. Mobile Phase B was used to clean the column after the thymol and propofol eluted using Mobile Phase A (4.2 and 7.4 minutes, respectively).

The dog exhibited signs of anesthesia upon injection of both formulations based on visual observations and EEG patterns. The dog recovered from anesthesia from both formulations in 20–30 minutes. Propofol blood levels resulting from injection of the propofol prodrug approximate those from injection of Diprivan®.

(5) Solubility Estimate of Camptothecin prodrug in water

The water solubility of the camptothecin prodrug is greater than 50 mg/mL based on visual and HPLC analysis.

(6) Camptothecin Prodrug (p-cpt) Enzymatic Study

A 16 μg/mL p-cpt was cleaved with acid phosphatase (0.02 units/mL of p-cpt solution). The media was 0.09M citrate buffer, pH 4.8 and the temperature was 37° C. The conversion of p-cpt to camptothecin was monitored by HPLC.

HPLC Parameters:

MP: 24% potassium phosphate buffer pH 4, 76% acetonitrile

Column: Zorbax RX-C18, 15 cm×4.6 mm i.d., 5 μm particle size

Detection: 370 nm UV

Flowrate: 1 mL/min

Acid phosphatase from bovine prostate (sigma). The results are shown in FIG. 3. The results demonstrate that the camptothecin prodrug is a substrate for phophatases.

(7) Pharmacokinetic Study of the Camptothecin Prodrug Using Rats

Pharmacokinetic experiments involving the dosing of male Sprague-Dawley rats with formulations of the camptothecin prodrug and camptothecin were undertaken. The two formulations of the camptothecin prodrug that were examined consisted of the prodrug dissolved in 15 mM phosphate, pH 4.0 and camptothecin dissolved in organic co-solvents. The following is a summary of the pharmacokinetic experiments:

A volume of the camptothecin prodrug formulation or camptothecin formulation was prepared at a concentration so that a dose equivalent to 1 mg camptothecin per kg weight could be given to the rat. The formulation was given to the rat using an indwelling cannula in the left jugular vein of the rat. Blood samples were taken via an indwelling cannula located in the right jugular vein of the rat. Both cannulas were rinsed with heparinized saline prior to use and contained heparinized saline during the study.

The rats were anesthetized with sodium pentobarbital prior to insertion of the jugular cannulas and kept anesthetized with sodium pentobarbital during the study. The rats were placed on a 37° C. heating pad during the study and tracheotomized. Blood samples of approximately 150 μL were taken prior to dosing and after 1, 3, 5, 10, 15, 20, 30, 45, 60 and 90 minutes after the formulations were given to the rat.

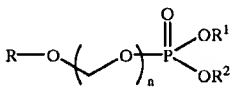
The blood samples were placed in microcentrifuge tubes and centrifuged for 20 seconds at approximately 15000 rpm. A 50 μL aliquot of plasma from each blood sample was transferred to a second microcentrifuge tube. A 150 μL aliquot of chilled acetonitrile was added to the plasma and the preparation is vortexed for 5 seconds. A 450 μL aliquot of chilled sodium phosphate (0.1M, pH 7.2) was then added. The contents in the microcentrifuge tubes were vortexed for 5 seconds and centrifuged for 20 seconds at approximately 15000 rpm. The supernatant was transferred to an HPLC autosampler set at 4° C. and analyzed (50 μL injections).

The HPLC system consisted of the following Shimadzu components: LC-10AT pump, SCL-10A system controller, RF 535 fluorescence detector, SIL-10A autosampler (set at 4° C.), and CTO-10A column oven (temperature set at 30° C.). The HPLC parameters were as follows: excitation at 370 nm and emission at 435 nm; flow rate at 2 mL/min. The HPLC column was a Hypersil ODS, 15 cm×4.5 mm i.d., 5 μm particle size. The mobile phase was 75% 25 nM sodium phosphate, pH 6.5/25% acetonitrile (v/v) with 25 mM tetrabutylammonium dihydrogen phosphate added as an ion-impairing reagent.

As can be seen in the graph (FIG. 4) the prodrug provides camptothecin plasma levels which are equivalent a to those attained from direct injection of camptothecin in organic co-solvents. The graph provides the mean with standard deviation for five rats which received prodrug and six rats which received camptothecin.

We claim:

1. A compound according to formula I:



I

wherein,

R—O— is a residue of a phenol containing pharmaceutical compound,

R^1 Is hydrogen or an alkali metal ion or a protonated amine or a protonated amino acid,

R^2 is hydrogen or an alkali metal ion or a protonated amine or a protonated amino acid, and

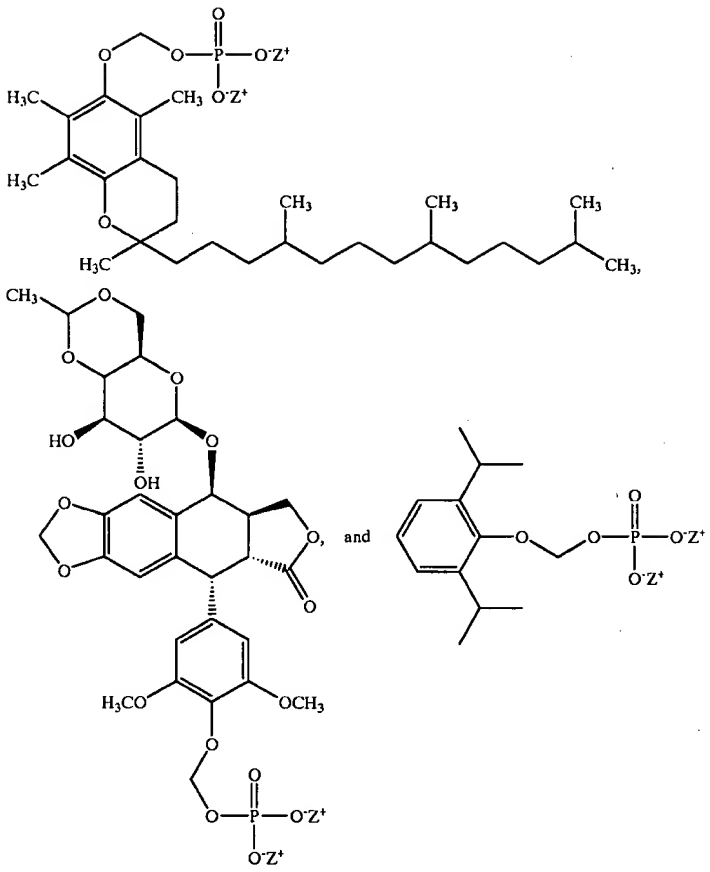
n is an integer of 1 or 2;

and pharmaceutically acceptable salts thereof.

2. The compound according to claim 1, wherein said phenol-containing compound is selected from the group consisting of propofol, etoposide, and vitamin E.

3. The compound according to claim 1, wherein the alkali metal ion of R^1 and R^2 is each independently selected from the group consisting of sodium, potassium and lithium.

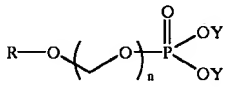
4. A compound selected from the group consist of:



wherein Z is selected from the group consisting of hydrogen, alkali metal ion, and anine; and pharmaceutically acceptable salts thereof.

5. The compound according to claim 4, wherein each Z is independently selected from the group consisting of sodium, tromethamine, triethanolamine, triethylamine, arginine, lysine, ethanolamine and N-methylglucamine.

6. A compound according to formula IV:



(IV)

wherein,

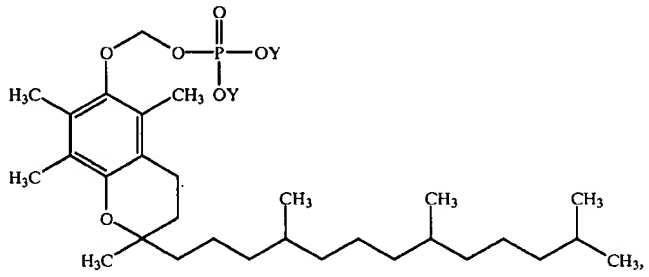
R—O— is a residue of a phenol-containing pharmaceutical compound,

Y is a phosphono protecting group, and

n is an integer of 1 or2;

and pharmaceutically acceptable salts thereof.

7. A compound according to claim 6, wherein said compound is selected from the group consisting of:



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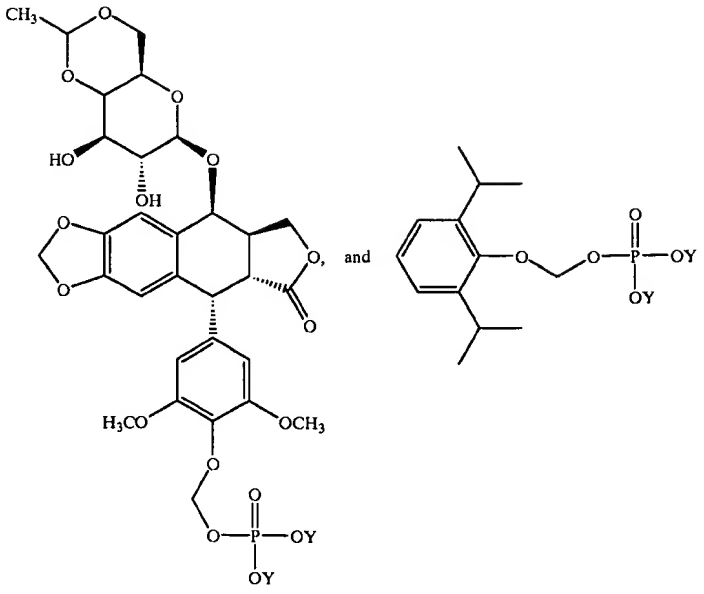


wherein Y is a phosphono protecting group.

8. The compound according to claim **6**, wherein said phosphono protecting group is selected from the group consisting of a benzyl group, a t-butyl group, an allyl group, and other acceptable phosphate protecting groups.

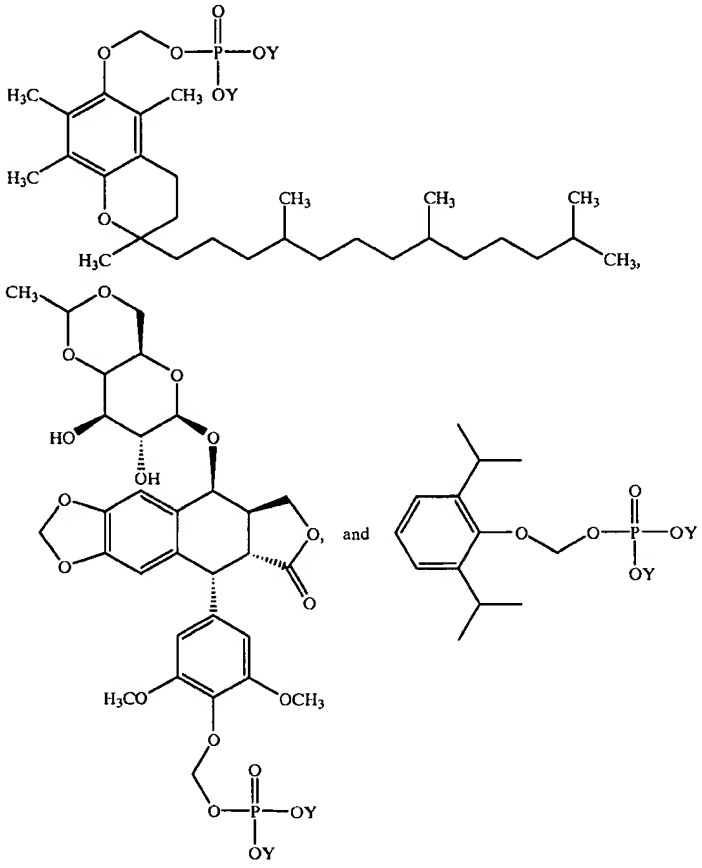
9. A pharmaceutical composition, comprising:

a compound according to claim **1**; and

a pharmaceutically acceptable carrier.

10. A process for preparing a compound of claim **4**, comprising:

removing a phosphono protecting group from a compound according to one of the following formula:



wherein Y is the phosphono protecting group; and recovering the product.

11. A method of treatment which produces an anesthetic effect comprising administering to a patient in need thereof an effective amount of a composition according to claim **1**.

12. The method according to claim **11**, wherein said compound is administered orally.

13. The method according to claim **11**, wherein said compound is administered parenterally.

14. The compound according to formula I,

I

wherein,

R—O is a residue of propofol,

R^1 is hydrogen or an alkali metal ion or a protonated amine or a protonated amino acid,

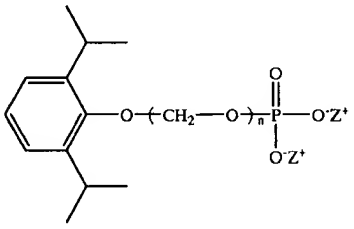
R^2 is hydrogen or an alkali metal ion or a protonated amine or a protonated amino acid, and

n is an integer of 1 or 2;

and pharmaceutically acceptable salts thereof.

15. The compound according to claim **14**, wherein the alkali metal ion of R^1 and R^2 is independently selected from the group consisting of sodium, potassium and lithium.

16. A compound

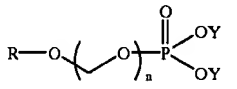


wherein Z is selected from the group consisting of hydrogen, alkali metal ion and amine, and n is an integer of 1 or 2; and pharmaceutically acceptable salts thereof.

17. The compound according to claim **16**, wherein Z is independently selected from the group consisting of sodium, tromethamine, triethanolamine, triethylamine, arginine, lysine, ethanolamine and N-methylaglucamine.

18. The compound according to Formula I,

(IV)



wherein

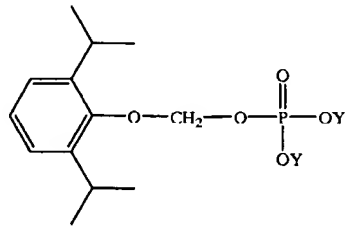
R—O is a residue of propofol

Y is a phosphono protecting group, and

n is an integer of 1 or 2;

and pharmaceutically acceptable salts thereof.

19. A compound:



wherein Y is a phosphono protecting group.

20. The compound according to claim **19**, wherein said phophonoprotecting group is selected from the group consisting of a benzyl group, a t-butyl group, an allyl group, and other acceptable phosphate protecting groups.

21. A pharmaceutical composition comprising an effective anesthetic amount of the compound according to claim **14** and a pharmaceutically acceptable carrier.

22. A method of treatment which produces an anesthetic effect comprising administering to a patient in need thereof an effective anesthetic amount of the composition of claim **21**.

23. A pharmaceutical composition comprising an effective anesthetic amount of the compound according to any one of claims **15–20** and a pharmaceutically acceptable carrier.

24. A method of producing an anesthetic effect which comprises administering to a patient in need thereof an effective anesthetic amount of the compound according to any one of claims **14–20**.

25. A pharmaceutical composition comprising an effective anti-cancer amount of the compound according to any one of claims **1–5**, **8**, **9** or **10** and a pharmaceutically acceptable carrier, wherein said pharmaceutical compound is etoposide.

26. A method of treating cancer which comprises administering to a patient in need thereof an effective anti-cancer amount of the compound according to any one of claims **1–5**, **8**, **9** or **10** wherein said pharmaceutical compound is etoposide.

27. A pharmaceutical composition comprising a pharmaceutical compound according to any one of claims **1–5**, **8**, **9** or **10** and a pharmaceutically acceptable carrier, wherein said pharmaceutical compound is vitamin E.

28. A method of treating vitamin E deficiency which comprises administering to a patient in need thereof an effective amount of the compound according to any one of claims **1–5**, **8**, **9** or **10**, wherein said pharmaceutical compound is Vitamin E.

* * * * *

Exhibit 2

01-20-1999

Docket No.: 1257-116P

FORM [illegible] (Modified)
(Rev [illegible])
OMB [illegible]
Copyright [illegible] LaserStar
PO#R: V02

[illegible]EET U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

100944915

Tab settings ▼ ▼ ▼ ▼ ▼ ▼ ▼

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof

1 Name of conveying party(ies):
Valentino J. STELLA
Jan J. ZYGMUNT
Ingrid Gunda GEORG
Muhammad S. SAFADI

Additional name(s) of conveying party(ies) ☐ Yes ☒ No

3 Nature of conveyance MRD 1-14-99

☒ Assignment ☐ Merger

☐ Security Agreement ☐ Change of Name

☐ Other

Execution Date: September 8 and 28, 1998

2. Name and address of receiving party(ies):

Name: University of Kansas

Internal Address: Center for Drug Delivery Research

RECEIVED

Street Address: 2095 Constant Avenue

City: Lawrence State: KS ZIP: 66047

Additional name(s) & address(es) attached? ☐ Yes ☒ No

4 Application number(s) or registration numbers(s):

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s)

09/131,385

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

5 Name and address of party to whom correspondence concerning document should be mailed:

Name: BIRCH, STEWART, KOLASCH & BIRCH, LLP

Internal Address:

Street Address: P.O. BOX 747

01/19/1999 DNGUYEN 00000226 09131385
01 FC:581 40.00 OP

City: FALLS CHURCH State: VA ZIP: 22040

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41):.....$ 40.00

☒ Enclosed - Any excess or insufficiency should be credited or debited to deposit account

☐ Authorized to be charged to deposit account

8. Deposit account number:

02-2448

DO NOT USE THIS SPACE

9 Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Leonard R. Svensson, Reg. No. 30,330 — January 7, 1999

Name of Person Signing — Signature — Date

Total number of pages including cover sheet, attachments, and document: 3

BIRCH, STEWART, KOLASCH & BIRCH, LLP
United States Patent Rights, or
United States plus All Foreign Patent Rights

ATTORNEY DOCKET NO.
1257-116P

ASSIGNMENT

Application No. ~~XXXX~~ 09/131,385 Filed Aug. 7, 1998

Insert Name(s) of Inventor(s) ➡ WHEREAS,

Valentino J. STELLA, Jan J. ZYGMUNT, Ingrid Gunda GEORG,

Muhammad S. SAFADI

(hereinafter designated as the undersigned) has (have) invented certain new and useful improvements in

Insert Title of Invention ➡ WATER SOLUBLE PRODRUGS OF HINDERED ALCOHOLS

for which an application for Letters Patent of the United States of America has been executed by the undersigned

Insert Date of Signing of Application ➡ on September 8 and 28, 1998; and

Insert Name of Assignee ➡ WHEREAS, University of Kansas

Insert Address of Assignee ➡ of Center for Drug Delivery Research

2095 Constant Avenue Lawrence, Kansas 66047-3729

its heirs, successors, legal representatives and assigns (hereinafter designated as the Assignee) is desirous of acquiring the entire right, title and interest in and to said invention and in and to any Letters Patent(s) that may be granted therefor in the United States of America and

CHECK BOX IF APPROPRIATE ➡ [ ] in any and all foreign countries.

NOW, THEREFORE, in consideration of the sum of Ten Dollars ($10.00) to the undersigned in hand paid, the receipt of which is hereby acknowledged, and other good and valuable consideration, the undersigned has (have) sold, assigned and transferred, and by these presents does sell, assign and transfer unto said Assignee the full and exclusive right to the said invention in the United States of America, its territories, dependencies and possessions and the entire right, title and interest in and to any and all Letters Patent(s) which may be granted therefor in the United States of America, its territories, dependencies and possessions, and if the box above is designated, in any and all foreign countries;

and to any and all divisions, reissues, continuations and extensions thereof for the full term or terms for which the same may be granted.

The undersigned agree(s) to execute all papers necessary in connection with this application, and any continuing, divisional or reissue applications thereof and also to execute separate assignments in connection with such applications as the Assignee may deem necessary or expedient.

The undersigned agree(s) to execute all papers necessary in connection with any interference which may be declared concerning this application or continuation, division or reissue thereof or Letter Patent(s) or reissue patent issued thereon and to cooperate with the Assignee in every way possible in obtaining and producing evidence and proceeding with such interference.

The undersigned agree(s) to execute all papers and documents and to perform any act which may be necessary in connection with claims or provisions of the International Convention for the Protection of Industrial Property or similar agreements.

The undersigned agree(s) to perform all affirmative acts which may be necessary to obtain a grant of a valid United States of America patent(s) or a grant of a valid United States of America and any foreign patent(s) to the Assignee and to vest all rights therein hereby conveyed to said Assignee as fully and entirely as the same would have been held by the undersigned if this Assignment and sale had not been made.

The undersigned hereby authorize(s) and request(s) the Patent and Trademark Office Officials in the United States of America and in any foreign countries to issue any and all Letters Patents resulting from said application or any continuing, divisional or reissue applications thereof to the said Assignee as Assignee of the entire interest, and hereby covenants that he has (they have) the full right to convey the entire interest herein assigned, and that he has (they have) not executed, and will not execute, any agreement in conflict herewith.

The undersigned hereby grant(s) the law firm of Birch, Stewart, Kolasch & Birch, LLP the power to insert on this Assignment any further identification which may be necessary or desirable in order to comply with the rules of the U.S. Patent and Trademark Office for recordation of this document.

The undersigned hereby covenant(s) that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment.

In witness whereof, executed by the undersigned on the date(s) opposite the undersigned name(s).

Date: Sept 8, 1998. Name of Inventor: Valentino J. Stella (signature) Valentino J. STELLA

Date: 98 SEP 08 Name of Inventor: [signature] (signature) Jan C. ZYGMUNT

Date: Sept 8, 1998. Name of Inventor: Ingrid Gunda Georg (signature) Ingrid Gunda GEORG

Date: Sept. 28, 1998 Name of Inventor: M. Safadi (signature) Muhammad S. SAFADI

Date: _____, Name of Inventor: _____ (signature)

Date: _____, Name of Inventor: _____ (signature)

Exhibit 3

Eisai Medical Research Inc.
55 Challenger Road
Ridgefield Park, New Jersey 07660
Telephone: 201 403-2500

hhc
human health care

Jacqueline M. Kline, PhD, PMP
Director, Regulatory Affairs
Eisai Medical Research, Inc.
6611 Tributary Street
Baltimore, MD 21224

February 4, 2009

VIA HAND DELIVERY

Mary C. Till
Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Re: *Patent Term Extension for Patent No. 6,204,257*

Dear Ms. Till:

On behalf of Eisai Medical Research Inc., Marketing Applicant for New Drug Application No. 22-244 for LUSEDRA™ (fospropofol disodium), its predecessors, and affiliates, I hereby authorize the patent owner of record, the University of Kansas, in connection with its application for extension of U.S. Patent No. 6,204,257, to rely upon the activities of Eisai Medical Research Inc., its predecessors, and affiliates, undertaken in connection with seeking approval by the Food and Drug Administration of NDA No. 22-244. Eisai Medical Research Inc. is a licensee of the University of Kansas under the patent.

Respectfully submitted,

Jacqueline M. Kline

Jacqueline M. Kline, PhD, PMP
Director, Regulatory Affairs

Exhibit 4

KU CENTER FOR TECHNOLOGY COMMERCIALIZATION
The University of Kansas

February 6, 2009

VIA HAND DELIVERY

Mary C. Till
Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA
22313-1450

Re: Patent Term Extension Applications for United States Patent Nos. 6,204,257 ("the '257 patent") and 6,872,838 ("the '838 patent")

Dear Ms. Till:

This is to advise you that, as an authorized representative of the University of Kansas (KU), owner of United States Patent Nos. 6,204,257 ("the '257 patent") and 6,872,838 ("the '838 patent"), I hereby authorize Eisai Medical Research Inc. of 6611 Tributary Street, Baltimore, Maryland, ("Eisai") to file and prosecute patent term extension applications pursuant to 35 U.S.C. § 156 for the '257 and '838 patents ("the Applications") on behalf of KU, pursuant to 37 CFR § 1.730(c). I understand that counsel for Eisai, Covington & Burling LLP, 1201 Pennsylvania Ave. N.W., Washington, D.C., 20004-2401 (C&B), will file and prosecute the Applications as Eisai's representative, pursuant to 37 C.F.R. § 1.730(c), and hereby grant C&B any authorizations from KU necessary for C&B to act in this capacity.

Sincerely,

James G. Baxendale MS, MBA
Executive Director, KU Center for
Technology Commercialization, Inc.

Exhibit 5

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LUSEDRA safely and effectively. See full prescribing information for LUSEDRA.

LUSEDRA (fospropofol disodium) Injection, for intravenous use
Initial U.S. Approval: 20XX

----------**INDICATIONS AND USAGE**----------
LUSEDRA is a sedative-hypnotic agent indicated for monitored anesthesia care (MAC) sedation in adult patients undergoing diagnostic or therapeutic procedures.(1)

----------**DOSAGE AND ADMINISTRATION**----------
- Use supplemental oxygen in all patients undergoing sedation with LUSEDRA (2.1). Continuously monitor with pulse oximetry, electrocardiogram, and frequent blood pressure measurements (5.1).
- Standard dosing regimen: initial intravenous bolus dose of 6.5 mg/kg followed by supplemental doses of 1.6 mg/kg as needed. No initial dose should exceed 16.5 mL; no supplemental dose should exceed 4 mL. (2.2)
- Modified dosing regimen [for patients who are ≥65 years of age or who have severe systemic disease (ASA P3 or P4)]: 75 % of the standard dosing regimen. (2.3)
- Administer supplemental doses only when patients can demonstrate purposeful movement in response to verbal or light tactile stimulation and no more frequently than every 4 minutes. (2.1)
- Adults who weigh >90 kg should be dosed as if they are 90 kg; adults who weigh <60 kg should be dosed as if they are 60 kg. (2.2)
- Intended for single use administration only.

----------**DOSAGE FORMS AND STRENGTHS**----------
Injection, solution containing 1,050 mg fospropofol disodium per 30 mL. (3)

----------**CONTRAINDICATIONS**----------
None

----------**WARNINGS AND PRECAUTIONS**----------
- **A person trained in the administration of general anesthesia and not involved in the conduct of the diagnostic/therapeutic procedure should manage treatment of patients with LUSEDRA. (5.1)**
- Respiratory depression (5.2)
- Hypoxemia (5.3)
- Hypotension (5.4)

----------**ADVERSE REACTIONS**----------
Most common adverse reactions (> 20 %) are paresthesia and pruritus. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Eisai, Inc. at 1-888-422-4743 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------**DRUG INTERACTIONS**----------
As with other sedative-hypnotic agents, LUSEDRA may produce additive cardio-respiratory effects when administered with other cardio-respiratory depressants such as benzodiazepines and narcotic analgesics. (7)

----------**USE IN SPECIFIC POPULATIONS**----------
- Patients ≥65 years of age should receive the modified dosing regimen. (2.3, 8.5)
- Patients with severe systemic disease (ASA P3 or P4) should receive the modified dosing regimen. (2.3)

See 17 for PATIENT COUNSELING INFORMATION.

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LUSEDRA™ (fospropofol disodium) injection is an intravenous sedative-hypnotic agent indicated for monitored anesthesia care (MAC) sedation in adult patients undergoing diagnostic or therapeutic procedures.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Guidelines

- Administer LUSEDRA intravenously as a bolus injection.
- Use supplemental oxygen for all patients undergoing sedation with LUSEDRA.
- Individualize the dosage of LUSEDRA and titrate to the level of sedation required for the procedure.
- In adults aged 18 to <65 years who are healthy or have mild systemic disease as categorized by the American Society of Anesthesiology (ASA P1 or P2), the standard dosing regimen of LUSEDRA should be followed [see *Standard Dosing Regimen for Sedation (2.2)*].
- In adults who are ≥ 65 years of age or who have severe systemic disease (ASA P3 or P4), the modified dosing regime should be followed [see *Modified Dosing Regimen for Sedation in Patients ≥ 65 years or Those with Severe Systemic Disease (2.3)*].
- Administer supplemental doses of LUSEDRA based on the patient's level of sedation and the level of sedation required for the procedure. Give supplemental doses only when patients can demonstrate purposeful movement in response to verbal or light tactile stimulation and no more frequently than every 4 minutes. Use only the minimum dosage required to facilitate the procedure.
- Consider the potential for worsened cardio-respiratory depression prior to using LUSEDRA concomitantly with other drugs that have the same potential (e.g., sedative-hypnotics or narcotic analgesics) *[see Warnings and Precautions (5.2, 5.3)]*.
- In clinical studies, an opioid premedication (fentanyl citrate 50 mcg intravenously) was administered five minutes prior to the initial dose of LUSEDRA.

2.2 Standard Dosing Regimen for Sedation

In adults aged 18 to <65 years who are healthy or have mild systemic disease (ASA P1 or P2) [1], the standard dosing regimen of LUSEDRA is an initial intravenous bolus of 6.5 mg/kg followed by supplemental doses of 1.6 mg/kg intravenous (25 % of initial dosage) as needed to achieve the desired level of sedation as shown in Table 1.

The dosage of LUSEDRA is limited by lower and upper weight bounds of 60 kg and 90 kg. Adults who weigh >90 kg should be dosed as if they weigh 90 kg. **No initial dose should exceed 16.5 mL; no supplemental dose should exceed 4 mL.** Adults who weigh <60 kg should be dosed as if they weigh 60 kg. Dosages lower than those specified for the lower weight limit may be used to achieve lesser levels of sedation. In clinical studies, an opioid premedication (fentanyl citrate 50 mcg IV) was administered five minutes prior to the initial dose of LUSEDRA.

Table 1. Standard Dosing Regimen, Adults 18 to <65 Years of Age Who are Healthy or Have Mild Systemic Disease (ASA P1 or P2)

	Initial Dose		Supplemental Dose No more frequently than every 4 min	
Weight (kg)	mg	mL	mg	mL
≤60	385	11	105	3
61 to 63	402.5	11.5	105	3

64 to 65	420	12	105	3
66 to 68	437.5	12.5	105	3
69 to 71	455	13	105	3
72 to 74	472.5	13.5	122.5	3.5
75 to 76	490	14	122.5	3.5
77 to 79	507.5	14.5	122.5	3.5
80 to 82	525	15	140	4
83 to 84	542.5	15.5	140	4
85 to 87	560	16	140	4
88 to 89	577.5	16.5	140	4
≥90	577.5	16.5	140	4
Doses in this table are rounded to the nearest half-milliliter volume to facilitate practical measurement , hence may differ slightly from the dose recommended on the basis of mg/kg.				

2.3 Modified Dosing Regimen for Sedation in Patients ≥65 years or Those with Severe Systemic Disease (ASA P3 or P4)

Adults ≥65 years of age or those with severe systemic disease (ASA P3 or P4) [1] should receive initial and supplemental intravenous dosages of 75 % of the standard dosing regimen, as presented in Table 2. LUSEDRA is administered intravenously as a bolus injection. In clinical studies, an opioid premedication (fentanyl citrate 50 mcg IV) was administered five minutes prior to the initial dose of LUSEDRA.

Table 2. Modified Dosing Regimen, Ages ≥ 65 Years Or Those with Severe Systemic Disease (ASA P3 or P4)

	Initial Dose		Supplemental Dose No more frequently than every 4 min	
Weight (kg)	**mg**	**mL**	**mg**	**mL**
≤60	297.5	8.5	70	2
61 to 62	297.5	8.5	70	2
63 to 64	315	9	87.5	2.5
65 to 66	315	9	87.5	2.5
67 to 69	332.5	9.5	87.5	2.5
70 to 73	350	10	87.5	2.5
74 to 77	367.5	10.5	87.5	2.5
78 to 80	385	11	105	3

81 to 84	402.5	11.5	105	3
85 to 87	420	12	105	3
88 to 89	437.5	12.5	105	3
≥90	437.5	12.5	105	3
Note: Doses in this table are rounded to the nearest half-milliliter volume to facilitate practical measurement, hence may differ slightly from the dose recommended on the basis of mg/kg.				

2.4 Preparation

LUSEDRA is provided as a ready to use formulation intended for single-patient use only. Prepare LUSEDRA following strict aseptic techniques. Draw LUSEDRA into sterile syringes immediately after vials are opened. Discard any unused portion at the end of the procedure.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use if there is evidence of particulate matter or discoloration.

LUSEDRA has been shown to be compatible with the following fluids:

- 5 % Dextrose Injection, USP
- 5 % Dextrose and 0.2 % Sodium Chloride, USP
- 5 % Dextrose and 0.45 % Sodium Chloride Injection, USP
- 0.9 % Sodium Chloride Injection, USP
- Lactated Ringer's Injection, USP
- Lactated Ringer's and 5 % Dextrose Injection, USP
- 0.45 % Sodium Chloride Injection, USP
- 5 % Dextrose, 0.45 % NaCl and 20 mEq KCl, USP

Do not mix LUSEDRA with other drugs or fluids prior to administration. LUSEDRA is not physically compatible with midazolam HCl or meperidine HCl, and compatibility with other agents has not been adequately evaluated.

Administer LUSEDRA through a secure, freely flowing, peripheral intravenous line using commonly available intravenous administration sets. Flush the infusion line with normal saline before and after administration of LUSEDRA.

LUSEDRA is not light sensitive. LUSEDRA does not need to be filtered before use.

3 DOSAGE FORMS AND STRENGTHS

Single-use vial contents: Solution for intravenous administration containing 35 mg of fospropofol disodium per mL (1,050 mg of fospropofol disodium in 30 mL).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Monitoring

LUSEDRA should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the diagnostic or therapeutic procedure. Sedated patients should be continuously monitored, and facilities for maintenance of a patent airway, providing artificial ventilation, administering supplemental oxygen, and instituting cardiovascular resuscitation must be immediately available. Patients should be continuously monitored during sedation and through the recovery process for early signs of hypotension, apnea, airway obstruction, and/or oxygen desaturation.

5.2 Respiratory Depression

LUSEDRA may cause loss of spontaneous respiration. Apnea was reported in 1/455 (< 1 %) patients treated with LUSEDRA using the standard or modified dosing regimen [see *Dosage and Administration (2.2, 2.3)*]. In patients treated with greater than the recommended LUSEDRA dose, apnea was reported in 14/556 (3 %).

Supplemental oxygen is recommended for all patients receiving LUSEDRA. Dosages of LUSEDRA must be individualized for each patient and titrated to effect [see *Dosage and Administration (2.1) and Clinical Pharmacology (12.2)*]. Use lower doses of LUSEDRA in patients who are ≥ 65 years of age or who have severe systemic disease [see *Dosage and Administration (2.3)*]. The additive cardio-respiratory effects of narcotic analgesics and sedative-hypnotic agents should be considered when administered concomitantly with LUSEDRA.

Patients should be assessed for their ability to demonstrate purposeful response while sedated with LUSEDRA as patients who are unable to do so may lose protective reflexes. Airway assistance maneuvers may be required in the management of respiratory depression (see Table 4).

5.3 Hypoxemia

LUSEDRA may cause hypoxemia detectable by pulse oximetry. Hypoxemia was reported in 20/455 (4 %) patients treated with LUSEDRA using the standard or modified dosing regimen [see *Dosage and Administration (2.2, 2.3)*]. Hypoxemia was reported among patients who retained the ability to respond purposefully to their health care provider following administration of LUSEDRA. Therefore, retention of purposeful responsiveness did not prevent patients from becoming hypoxemic following administration of LUSEDRA. In patients treated with greater than the recommended LUSEDRA dose, hypoxemia was reported in 151/556 (27 %).

The risk of hypoxemia is reduced by appropriate positioning of the patient, and the use of supplemental oxygen in all patients receiving LUSEDRA. Airway assistance maneuvers may be required in the management of hypoxemia (see Table 4). The additive cardio-respiratory effects of narcotic analgesics and other sedative-hypnotic agents should be considered when administered concomitantly with LUSEDRA.

5.4 Patient Unresponsiveness to Vigorous Tactile or Painful Stimulation

LUSEDRA has not been studied for use in general anesthesia. However, administration of LUSEDRA may inadvertently cause patients to become unresponsive or minimally responsive to vigorous tactile or painful stimulation. The incidence of patients sedated for colonoscopy who became minimally responsive or unresponsive to vigorous tactile or painful stimulation was 7/183 (4%). The duration of minimal or complete unresponsiveness in colonoscopy patients ranged from 2 to 16 minutes. Among patients sedated for bronchoscopy, the incidence of patients who became minimally or completely unresponsive to vigorous tactile or painful stimulation was 24/149 (16%). The duration of minimal to complete unresponsiveness in bronchoscopy patients ranged from 2 to 20 minutes.

5.5 Hypotension

Hypotension following the use of LUSEDRA may occur. Hypotension was reported in 18/455 (4 %) patients treated with LUSEDRA using the standard or modified dosing regimen [see *Dosage and Administration (2.2,2.3)*]. In patients treated with greater than the recommended LUSEDRA dose, hypotension was reported in 31/556 (6 %).

Patients with compromised myocardial function, reduced vascular tone, or who have reduced intravascular volume may be at an increased risk for hypotension. A secure intravenous access catheter and supplemental volume replacement fluids should be readily available during the procedure. Additional pharmacological management may be necessary.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Respiratory depression *[see Warnings and Precautions (5.2)]*
- Hypoxemia *[see Warnings and Precautions (5.3)]*
- Loss of purposeful responsiveness *[see Warnings and Precautions (5.4)]*
- Hypotension *[see Warnings and Precautions (5.5)]*

The most common adverse reactions (reported in greater than 20%) are paresthesia and pruritis.

The most commonly reported reasons for discontinuation are paresthesia and cough.

6.1 Clinical Trials Experience

Adverse reactions presented in this section are derived from 332 patients in 3 controlled clinical trials in patients undergoing colonoscopy or flexible bronchoscopy and 123 patients in one open-label study in patients undergoing minor procedures. Patients enrolled in the studies who received the standard or modified dosing regimen included males and females, ≥18 years of age and ranging from healthy (359/455 [79 %] ASA P1 or P2) to those with severe systemic disease (96/455 [21 %] ASA P3 or P4). Of the 455 patients enrolled, 345 (76 %) were ≥18 to <65 years of age and 110 (24 %) were ≥65 years of age. Adverse reactions are reported for patients who received the standard or the modified dosing regimen [see *Dosage and Administration (2)*]. The majority of procedures were less than thirty minutes in duration. All patients in these studies received 50 mcg fentanyl citrate intravenous as premedication and some of the patients received additional 25 mcg fentanyl citrate supplemental doses. Adverse reactions occurring in ≥2 % of patients in these studies are presented in Table 3.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not accurately reflect the rates observed in practice.

Table 3. Common Adverse Reactions for Patients Receiving the Standard or Modified Dosing Regimen (Reactions Occurring at a Rate ≥ 2%)

Reaction Term	Colonoscopy (N=183) n (%)	Minor Procedures (N=123) n (%)	Bronchoscopy (N=149) n (%)
Gastrointestinal disorders			
Nausea	0	5 (4)	2 (1)
Vomiting	0	4 (3)	0
Injury, poisoning, and procedural complications			
Procedural Pain	0	0	3 (2)
Nervous system disorders			
Paresthesia[a]	135 (74)	77 (63)	78 (52)
Headache	1 (1)	3 (2)	1 (1)
Respiratory, thoracic, and mediastinal disorders			
Hypoxemia	3 (2)	1 (1)	16 (11)
Skin and subcutaneous tissue disorders			
Pruritus[b]	30 (16)	34 (28)	24 (16)
Vascular disorders			

Hypotension	4 (2)	4 (3)	10 (7)

[a] Paresthesia includes the following terms: Paresthesia genital male; Burning sensation; Genital burning sensation; Vaginal burning sensation; Skin burning sensation; Genital pain (reported as burning); Perineal pain (reported as burning); Anal discomfort (reported as burning); Chest pain (reported as burning); Ear discomfort (reported as burning); Nasal discomfort (reported as burning); Buttock pain (reported as stinging); Groin pain (reported as stinging); Pain (reported as stinging); Sensory disturbance (reported as non-specific sensation in pubic area).

[b] Pruritus includes the following terms: Genital pruritus female; Genital pruritus male; Pruritus genital; Pruritus ani; Pruritus generalized

Paresthesias (including burning, tingling, stinging) and/or pruritus, usually manifested in the perineal region, were the most frequently recorded adverse reactions in clinical trials. Paresthesias and pruritus generally occurred within 5 minutes after administration of the initial dose of LUSEDRA and were generally transient and mild to moderate in intensity. The pharmacologic basis of these sensory phenomena is unknown. No pretreatments, including the use of nonsteroidal anti-inflammatory drugs, opioids, or lidocaine, are known to have an effect on, or to reduce the incidence of these sensations.

Sedation-related adverse reactions were experienced at the following rates for subjects receiving the standard or modified LUSEDRA dosing regimen: 20/455 (4 %) hypoxemia, 18/455 (4 %) hypotension, 1/455 (< 1 %) apnea. A greater rate of sedation-related adverse reactions necessitating intervention was observed in patients undergoing bronchoscopy compared with colonoscopy and minor surgical procedures. In the colonoscopy studies, 5/183 (3 %) patients were ASA P3. In the minor surgical procedures study, 23/123 (19 %) patients were ASA P3 or P4. In the flexible bronchoscopy study, 68/150 (46 %) patients were ASA P3 or P4. The type and incidence of airway assistance interventions required for patients who experienced sedation-related adverse reactions are presented in Table 4.

Table 4. Patient Incidence of Airway Management Events

	Healthy Subjects[a] 6 mg/kg N=69 n (%)	Colonoscopy[b] 6.5 mg/kg (or modified dosing regimen) N=183 n (%)	Minor Procedures[b] 6.5 mg/kg (or modified dosing regimen) N=123 n (%)	Flexible Bronchoscopy[b] 6.5 mg/kg (or modified dosing regimen) N=149 n (%)
Increased O_2	0	0	0	21 (14)
Patient Repositioning	0	0	0	2 (1)
Verbal Stimulation	0	2 (1)	1 (1)	5 (3)
Tactile Stimulation	0	0	0	3 (2)
Face Mask (100 % O_2)	0	0	0	1 (1)
Jaw Thrust	0	0	0	2 (1)
Chin Lift	0	0	1 (1)	3 (2)
Nasal Trumpet	0	0	0	0
Oral Airway	0	0	0	0
Suction	0	0	0	2 (1)
Manual Ventilation (bag valve mask)	0	0	0	1 (1)
Mechanical Ventilation	0	0	0	0

[a] No concomitant medications administered. All subjects were healthy volunteers.

[b] All patients premedicated with 50 mcg fentanyl citrate. Subjects ranged from healthy to those with severe systemic disease that is a constant threat to life (ASA P1 to P4).

6.2 Adverse Reactions in Prolonged Exposure in Adults

The safety of LUSEDRA for continuous sedation has not been established and therefore its use is not recommended. LUSEDRA was administered to 38 intubated and mechanically ventilated patients in post-operative and intensive care settings. An occurrence of nonsustained ventricular tachycardia was observed as a serious adverse reaction in one patient in the study. Another patient with acute myeloid leukemia with renal and hepatic insufficiency experienced a further increase in plasma formate concentration from a baseline of 66 mcg/mL to a post-dose level of 212 mcg/mL after a 12-hour infusion. The clinical significance of these findings is unknown.

7 DRUG INTERACTIONS

LUSEDRA may produce additive cardio-respiratory effects when administered with other cardio-respiratory depressants such as sedative-hypnotics and narcotic analgesics.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects:

Pregnancy Category B.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Reproduction studies have been performed in rats and rabbits at doses up to 0.6 and 1.7 times the anticipated human dose for a procedure of 16 minutes based on a comparison of doses expressed as mg/m^2 and have revealed no evidence of impaired fertility or harm to the fetus due to LUSEDRA.

Pregnant rats were treated with fospropofol disodium (5, 20, or 45 mg/kg/day, IV) from gestation day 7 through 17 (the highest dose is 0.6 times the anticipated human dose for a procedure of 16 minutes based on a comparison of doses expressed as mg/m^2). Doses of 20 and 45 mg/kg/day produced significant maternal toxicity. No drug-related adverse effects on embryo-fetal development were noted.

Pregnant rabbits were treated with fospropofol disodium (14, 28, 56 or 70 mg/kg/day, IV) from gestation day 6 through 18 (the highest dose is 1.7 times the anticipated human dose for a procedure of 16 minutes based on a comparison of doses expressed as mg/m^2). Significant maternal toxicity was noted at all doses. No drug-related adverse effects on embryo-fetal development were noted.

Nonteratogenic effects.

Pregnant rats were administered 0, 5, 10, or 20 mg/kg/day fospropofol disodium from gestation day 7 through lactation day 20 to evaluate perinatal and postnatal development (the highest dose is 0.2 times the anticipated human dose for a procedure of 16 minutes based on a comparison of doses expressed as mg/m^2). There were no clear treatment-related effects on growth, development, behavior (passive avoidance and water maze) or fertility and mating capacity of the offspring.

8.2 Labor and Delivery

LUSEDRA is not recommended for use in labor and delivery, including Cesarean section deliveries. It is not known if fospropofol crosses the placenta; however, propofol is known to cross the placenta, and as with other sedative-hypnotic agents, the administration of LUSEDRA may be associated with neonatal respiratory and cardiovascular depression.

8.3 Nursing Mothers

It is not known whether fospropofol is excreted in human milk; however, propofol has been reported to be excreted in human milk and the effects of oral absorption of fospropofol or propofol are not known. LUSEDRA is not recommended for use in nursing mothers.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established because LUSEDRA has not been studied in persons <18 years of age. LUSEDRA is not recommended for use in this population.

8.5 Geriatric Use

In studies of LUSEDRA for sedation in brief diagnostic and therapeutic procedures, 17 % patients were ≥65 years of age and 5 % of patients were ≥75 years of age. Patients ≥65 years of age should receive the modified dosing regimen [see *Dosage and Administration (2.3)*]. Hypoxemia was reported more frequently among patients aged ≥75 years than among patients aged 65 to <75 years and less frequently among younger patients, aged 18 to < 65 years.

8.6 Patients with Renal Impairment

In studies of LUSEDRA for sedation in brief diagnostic and therapeutic procedures, 21 % of patients had a creatinine clearance <80 mL/min and 4 % had a creatinine clearance <50 mL/min. Pharmacokinetics of fospropofol or propofol were not altered in patients with mild to moderate renal insufficiency. No dosing adjustments are required for patients with creatinine clearance ≥ 30 mL/min. Limited safety and efficacy data are available for LUSEDRA in patients with creatinine clearance < 30 mL/min.

8.7 Patients with Hepatic Impairment

LUSEDRA has not been adequately studied in patients with hepatic impairment. Caution should be exercised when using fospropofol disodium in patients with hepatic impairment.

9 DRUG ABUSE AND DEPENDENCE

9.1 Abuse

No formal studies of the abuse potential of LUSEDRA have been conducted. Administration of LUSEDRA resulted in euphoria in a small number of subjects who received intravenous or oral dosing.

9.2 Dependence

No formal studies of dependence have been conducted.

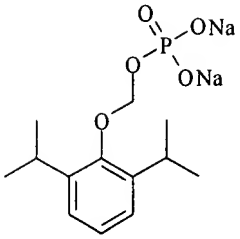
10 OVERDOSE

Overdosage with LUSEDRA can cause cardiorespiratory depression. If overdosage occurs, LUSEDRA administration should be discontinued immediately. Respiratory depression may require manual or mechanical ventilation. Cardiovascular depression may require elevation of lower extremities, intravascular volume replacement, and/or pharmacological management.

Formate and phosphate are metabolites of LUSEDRA and may contribute to signs of toxicity following overdosage. Signs of formate toxicity are similar to those of methanol toxicity and are associated with anion-gap metabolic acidosis. Intravenous exposure to a large amount of phosphate could potentially cause hypocalcemia with paresthesia, muscle spasms, and seizures.

11 DESCRIPTION

LUSEDRA is an injection solution intended for intravenous administration as a sedative-hypnotic agent. LUSEDRA is an aqueous, sterile, nonpyrogenic, clear, colorless, iso-osmotic solution containing 35 mg/mL of fospropofol disodium. Fospropofol disodium is a water-soluble prodrug of propofol, chemically described as 2,6-diisopropylphenoxymethyl phosphate, disodium salt. The structural and molecular formulas are shown in Figure 1.



Molecular Formula: $C_{13}H_{19}O_5PNa_2$
Molecular Weight: 332.24
Figure 1. Structural and Molecular Formulas of Fospropofol Disodium

The inactive components include, monothioglycerol (0.25 wt%) and tromethamine (0.12 wt%). LUSEDRA has a pH of 8.2 to 9.0. LUSEDRA does not contain any antimicrobial preservatives and is intended for single-use administration.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fospropofol disodium is a prodrug of propofol. Following intravenous injection, fospropofol is metabolized by alkaline phosphatases. For every millimole of fospropofol disodium administered, one millimole of propofol is produced (1.86 mg of fospropofol disodium is the molar equivalent of 1 mg propofol).

12.2 Pharmacodynamics

The pharmacology of fospropofol, once metabolized to propofol, is comparable to that of propofol lipid emulsion, however, the liberation of propofol from fospropofol results in differences in the timing of the pharmacodynamic effects. To characterize the pharmacokinetic/pharmacodynamic (PK/PD) profile of propofol derived from LUSEDRA, 12 healthy subjects were administered a 10 mg/kg intravenous bolus dose of LUSEDRA and the sedative effect was measured as a decrease in Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score (Table 5).[2] The PK and PD results are shown in Figure 2. Peak plasma levels of propofol (2.2 ± 0.4 µg/mL) released from fospropofol were noted by 8 min (range 4 - 13 min) and minimum mean MOAA/S score of 1.2 (range 0 - 3) was noted in 7 min (range 1 - 15). Subjects completely recovered from sedative effects between 21 - 45 minutes after LUSEDRA administration.

Table 5. Modified Observer's Assessment of Alertness/Sedation Scale[2]

Responsiveness	Score
Responds readily to name spoken in normal tone	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Responds only after painful trapezius squeeze	1
Does not respond to painful trapezius squeeze	0

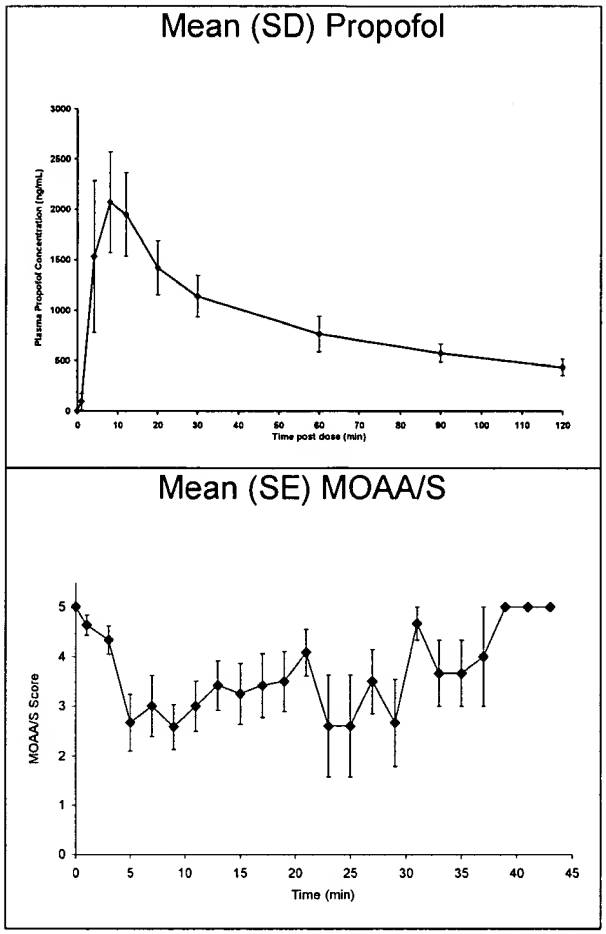


Figure 2. Pharmacokinetic and Pharmacodynamic Profiles after a 10 mg/kg Bolus Dose of LUSEDRA

LUSEDRA was evaluated in randomized, blinded, dose-controlled studies for sedation in patients undergoing colonoscopy and flexible bronchoscopy [see *Clinical Studies (14.1)*]. Figure 3 shows MOAA/S scores over time in each of the studies for those patients who received the standard and modified dosing regimens. In the study of patients undergoing colonoscopy, patients who received the standard and modified dosing regimens had a median [range] time to sedation (time from first dose of sedative to the first of 2 consecutive MOAA/S scores of ≤ 4) of 8.0 [2, 28] minutes and a median time to Fully Alert (3 consecutive responses to their name spoken in a normal tone, measured every 2 minutes beginning at or after the end of the procedure) of 5.0 [0, 47] minutes. In the study of patients undergoing flexible bronchoscopy, patients who received the standard and modified LUSEDRA dosing regimens had a median time to sedation of 4 [2, 22] minutes and a median time to Fully Alert of 5.5 [0, 61] minutes.

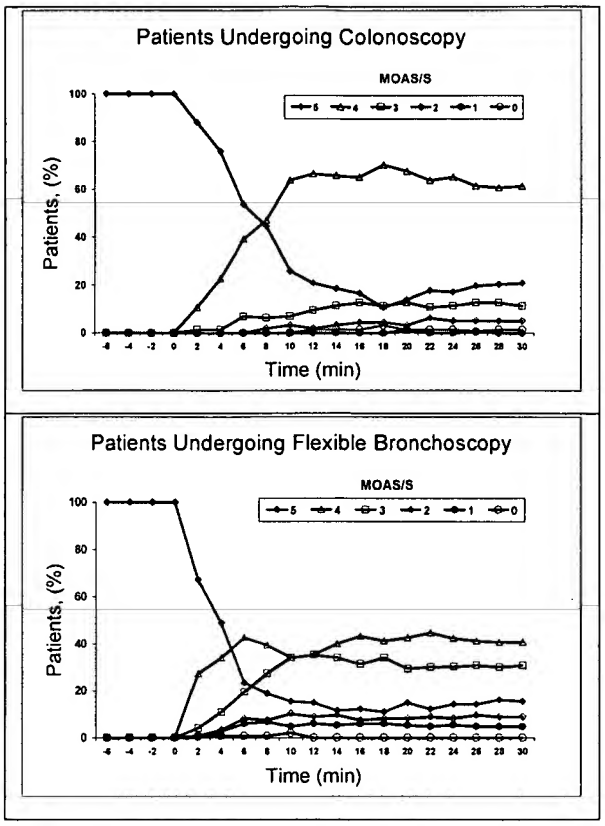


Figure 3. Percentage of Patients at Each MOAA/S Score Over Time

Within the recommended dose range, there were no differences in matched QTc interval changes between LUSEDRA and placebo. The effect of LUSEDRA on the QTcF interval was measured in a crossover study in which healthy subjects (n=68) received the following treatments: 6 mg/kg intravenous LUSEDRA; 18 mg/kg intravenous LUSEDRA; moxifloxacin 400 mg orally (positive control); and normal saline IV. After baseline and placebo adjustment, the maximum mean QTcF change was 2 ms (1-sided 95% Upper CI: 6 ms) for the 6 mg/kg dose and 8 ms (1-sided 95% Upper CI: 12 ms) for the 18 mg/kg dose. Used as a positive control, moxifloxacin had a maximum mean change in QTcF of 12 ms (1-sided 95% Lower CI: 6 ms).

12.3 Pharmacokinetics

PK parameters were evaluated in a cross-over study of 68 healthy subjects, 18 to 45 years of age, who received 6 and 18 mg/kg intravenous bolus doses of LUSEDRA. PK parameters are shown in Table 5. The C_{max} and $AUC_{0-\infty}$ values of fospropofol were dose proportional. The intersubject variability in C_{max} and $AUC_{0-\infty}$ was low. Propofol was rapidly liberated reaching plasma C_{max} at a median T_{max} of 12 minutes for LUSEDRA 6 mg/kg and 8 minutes for LUSEDRA 18 mg/kg. Concentration-time profiles showed a biexponential decline. The increase in C_{max} and $AUC_{0-\infty}$ of propofol was dose proportional.

Table 5. Pharmacokinetics Parameters (mean±SD) for Fospropofol and Propofol from LUSEDRA Administration

	Fospropofol			Propofol from LUSEDRA		
Parameter	Healthy (6 mg/kg) N=68	Healthy (18 mg/kg) N=68	Patient (6.5 mg/kg) N=667	Healthy (6 mg/kg) N=68	Healthy (18 mg/kg) N=68	Patient (6.5 mg/kg) N=400
C_{max} (mcg/mL)	78.7±15.4	211±48.6	--	1.08±0.33	3.90±0.822	--

T_{max} (min)	4	2	--	12	8	--
$AUC_{0-\infty}$ (mcg•h/mL)	19.2±3.59	50.3±8.4	19.0±7.2	1.70±0.29	5.67±1.28	1.2±0.39
CLp (L/h/kg)	0.28±0.053	0.32±0.058	0.36±0.16	1.95±0.34	1.79±0.39	3.2±0.92
$t_{1/2}$ (h)	0.81±0.08	0.81±0.09	0.88±0.08	2.06±0.77	1.76±0.54	1.13±0.28

Distribution

Fospropofol has a low volume of distribution of 0.33±0.069 L/kg and the liberated propofol has a large volume of distribution (5.8 L/kg).

Both fospropofol and its active metabolite propofol are highly protein bound (approximately 98 %), primarily to albumin. Fospropofol does not affect the binding of propofol to albumin.

Metabolism

Fospropofol is completely metabolized by alkaline phosphatases to propofol, formaldehyde, and phosphate. Formaldehyde and phosphate plasma concentrations are comparable to endogenous levels when fospropofol disodium is administered as recommended. Formaldehyde is further metabolized to formate by several enzyme systems, including formaldehyde dehydrogenase, present in various tissues. Propofol liberated from fospropofol is further metabolized to major metabolites propofol glucuronide (34.8 %), quinol-4-sulfate (4.6 %), quinol-1-glucuronide (11.1 %), and quinol-4-glucuronide (5.1 %). Oxidation to CO_2 is the primary means of eliminating excess formate.

Fospropofol is not a substrate of CYP450 enzymes.

Elimination

After a single 400 mg intravenous dose of [^{14}C]-fospropofol disodium in humans, approximately 71 % of radioactivity was recovered in the urine within 192 hours. Total body clearance (CL_p) of fospropofol was 0.280±0.053 L/h/kg and renal elimination of fospropofol was insignificant (<0.02 % of dose). The terminal phase elimination half-life ($t_{1/2}$) of fospropofol was 0.81±0.08 and 0.88±0.08 hours in healthy subjects and patients, respectively. In healthy subjects, the apparent total body clearance of liberated propofol (CL_p/F) was 1.95±0.345 L/h/kg and $t_{1/2}$ was 2.06±0.77 hours. In patients, the CLp of fospropofol was 0.31±0.14 L/h/kg and CLp/F for propofol was 2.74±0.80 L/h/kg and is similar to that observed in healthy subjects.

Special Populations

Population pharmacokinetic analysis indicated no influence of race, gender, age, renal impairment or alkaline phosphatase concentrations on the pharmacokinetics of fospropofol. Pharmacokinetics of propofol derived from fospropofol was not influenced by race, gender, or renal impairment.

LUSEDRA has not been adequately studied in patients with hepatic impairment. Caution should be exercised when using fospropofol disodium in patients with hepatic impairment.

Drug Interactions

There was no effect of analgesic premedication [fentanyl (1 mcg/kg); meperidine (0.75 mg/kg); midazolam (0.01 mg/kg); morphine (0.1 mg/kg)] on plasma pharmacokinetics of fospropofol.

In an in vitro protein binding study there was no significant interaction between fospropofol and propofol at concentrations up to 200 mcg/mL and 5 mcg/mL, respectively. The interaction of fospropofol with other highly protein-bound drugs given concomitantly has not been studied.

Potential of fospropofol or its major metabolite, propofol, to inhibit or induce major cytochrome P450 enzymes is not known.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis:
Long-term studies in animals have not been performed to evaluate the carcinogenic potential of fospropofol disodium.

Mutagenesis:
Fospropofol was not genotoxic in the Ames bacterial reverse mutation assay, with or without metabolic activation, and in the in vivo mouse micronucleus assay. Fospropofol was positive in the L5178Y $TK^{+/-}$ mouse lymphoma forward mutation assay in the presence of metabolic activation. In contrast, fospropofol was negative in this assay in the presence of formaldehyde-metabolizing enzymes suggesting that the positive finding is likely due to an artifact of the culture conditions.

Impairment of Fertility:
Male rats were treated with 5, 10, or 20 mg/kg fospropofol for 4 weeks prior to mating. Male fertility was not altered in animals treated with 20 mg/kg (0.3-fold the total human dose for a procedure of 16 minutes based on a mg/m^2 basis).

Female rats were treated with 5, 10, or 20 mg/kg fospropofol for two weeks prior to mating. There were no clear treatment-related effects on female fertility at a dose of 20 mg/kg (0.3-fold the total human dose for a procedure of 16 minutes based on a mg/m^2 basis).

14 CLINICAL STUDIES

14.1 Use in Sedation for Diagnostic or Therapeutic Procedures

The standard and modified LUSEDRA dosing regimens were evaluated in two controlled studies in patients dosed with LUSEDRA who were over 18 years of age and undergoing diagnostic or therapeutic, procedures. All patients received 50 mcg of fentanyl citrate intravenously before study sedative medication. The primary endpoint was the rate of "sedation success," defined as the proportion of patients who did not respond readily to their name spoken in a normal tone of voice (Modified Observer's Assessment of Alertness/Sedation Scale score of 4 or less) on 3 consecutive measurements taken every 2 minutes and who completed the procedure without the use of alternative sedative medication and without the use of manual or mechanical ventilation. [2]

In both studies, an initial bolus dose and up to 3 supplemental doses at 25 % of the initial bolus of study sedative medication was administered intravenously to sedate patients so that they did not respond readily to their name spoken in a normal tone and to allow the investigator to start the procedure. During the procedure supplemental doses at 25 % of the initial bolus were allowed to maintain sedation. Patients who were not adequately sedated with study drug received alternative sedative medication per the site's standard of care; however, sites were instructed not to use propofol as it would interfere with PK measurements.

The standard and modified LUSEDRA dosing regimens were evaluated in a randomized, blinded, dose-controlled study for sedation in patients undergoing colonoscopy. All of the patients who received alternative sedative medication (n=19) received midazolam. Patients randomized to receive the LUSEDRA standard or modified dosing regimen had a sedation success rate of 87% and required a mean number of supplemental doses of 2.3 ($\pm$1.4 SD). Patients randomized to receive LUSEDRA had median procedure durations of 11 minutes.

The standard and modified LUSEDRA dosing regimens were also evaluated in a randomized, blinded, dose-controlled study for sedation in patients undergoing flexible bronchoscopy. All of the patients who received alternative sedative medication (n=12), received midazolam. Patients randomized to receive the LUSEDRA standard or modified dosing regimen had a sedation success rate of 89 % and required a mean number of supplemental doses of 1.7 ($\pm$1.6 SD). Patients randomized to LUSEDRA had a median procedure duration of 10 minutes

15 REFERENCES

1. Kost, Michael. Moderate Sedation/Analgesia: Core Competencies for Practice. Elsevier Health Sciences, 2004. pp 62-63.
2. Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB, et al. Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. J Clin Psychopharmacol. 1990; 10(4):244-51.

16 HOW SUPPLIED/STORAGE AND HANDLING

LUSEDRA, 35 mg/mL (total of 1,050 mg/30 mL) fospropofol disodium, is supplied as a single-use, aqueous, sterile, nonpyrogenic, clear, colorless solution in glass vials ready for intravenous injection. Each vial is filled with 32.1 mL intended to deliver a minimum of 30 mL of fospropofol disodium solution. Store at controlled room temperature 25 °C (77 °F). Excursions permitted between 15° and 30 °C (59 ° and 86 °F).

NDC 62856-350-01.

17 PATIENT COUNSELING INFORMATION

Paresthesias (including burning, tingling, stinging) and/or pruritus, usually manifested in the perineal region are frequently experienced upon injection of the initial dose of LUSEDRA. Inform the patient that these sensations are typically mild to moderate in intensity, last a short time, and require no treatment.

Requirement for a patient escort should be considered. The decision as to when patients who have received LUSEDRA, particularly on an outpatient basis, may again engage in activities requiring complete mental alertness, coordination and/or physical dexterity (e.g. operate hazardous machinery, sign legal documents or drive a motor vehicle) must be individualized.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-244

NDA APPROVAL

Eisai Medical Research Inc.
6611 Tributary Street
Baltimore, MD 21224-6515

Attention: Jacqueline M. Kline, Ph.D.
Director, Regulatory Affairs

Dear Dr. Kline:

Please refer to your new drug application (NDA) dated September 26, 2007, received September 27, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lusedra (fospropofol disodium) Injection, 35mg/mL.

We acknowledge receipt of your submissions dated September 26, and November 5, 7, 16, and 30, 2007, and January 3, February 15, 26, and 29, March 6, 21, and 28, April 7 and 15, May 15, 21, and 30, June 6 and 27, October 23 and 24, and December 9 and 12, 2008.

The October 13, 2008, submission constituted a complete response to our July 23, 2008, action letter.

This new drug application provides for the use of Lusedra (fospropofol disodium) Injection for monitored anesthesia care (MAC) sedation in adult patients undergoing diagnostic or therapeutic procedures.

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert) submitted December 12, 2008. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, designate this submission, "**SPL for approved NDA 22-244.**"

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your December 12, 2008, submission containing final printed carton and container labels.

CONTROLLED SUBSTANCE SCHEDULING

We have recommended that this product be scheduled under the Controlled Substances Act. We remind you of the following statement that appears on the Form FDA 356h, "If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision." Once a final scheduling decision is made, your label must be amended to reflect the schedule. Submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. For administrative purposes, designate this submission, "**SPL for approved NDA 22-244.**" Approval of this submission by FDA is not required before the labeling is used.

In addition, submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels except for the addition of the scheduling mark as soon as they are available, but no more than 30 days after they are printed. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-244.**" Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring pediatric clinical trials in all age groups until April 1, 2012. Pediatric clinical trials in neonates, infants, and children under the age of three years are deferred until nonclinical studies of developing animals undergoing rapid synaptogenesis can be evaluated for possible accelerated apoptosis of the central nervous system associated with Lusedra and additional safety and effectiveness data have been collected. This delay will allow for accumulation of additional safety information from both the nonclinical juvenile program and the adult postmarketing database prior to initiation of investigation in pediatric patients. We are deferring submission of your pediatric studies in patients over the age of three years because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric clinical trials required under section 505B(a) of the FDCA are required postmarketing clinical trials. The status of these post-marketing clinical trials must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

1. Randomized, double-blind, dose-controlled clinical trial of fospropofol disodium injection in adolescent patients (12 through 18 years old) undergoing upper endoscopy. Pharmacokinetics will be studied using a population PK approach.

   You will conduct this trial according to the following timetable:

Protocol Submission:	by October 1, 2009
Study Start Date:	by March 1, 2010
Final Report Submission:	by April 1, 2012

2. Randomized, double-blind, dose-controlled clinical trial of fospropofol disodium injection in children (ages 3 up to 12 years old) undergoing sedation for magnetic resonance imaging (MRI). Pharmacokinetics will be studied using a population PK approach.

   You will conduct this trial according to the following timetable:

Protocol Submission:	January 1, 2012
Study Start Date:	June 1, 2012
Final Report Submission:	July 1, 2014

3. Randomized, double-blind, dose-controlled clinical trial of fospropofol disodium injection in infants and very young children (ages one month up to three years old) undergoing sedation for procedures such as lumbar puncture and/or MRI. Pharmacokinetics will be studied using a population PK approach.

   You will conduct this trial according to the following timetable:

Protocol Submission:	April 1, 2014
Start Date:	September 1, 2014
Final Report Submission:	August 1, 2016

4. Randomized, double-blind, dose-controlled clinical trial of fospropofol disodium injection in neonates (less than one month of age) undergoing sedation for procedures such as lumbar puncture, MRI, and/or circumcision. Pharmacokinetics will be studied using a population PK approach.

   You will conduct this trial according to the following timetable:

Protocol Submission:	October 1, 2014
Start Date:	October 1, 2016
Final Report Submission:	April 1, 2018

Submit final study reports to your NDA 22-244. For administrative purposes, all submissions related to these required pediatric postmarketing clinical trials must be clearly designated **"Required Pediatric Assessment(s)."**

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of Food and Drug Administration Amendments Act of 2007 (FDAAA) also amends the FDCA to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)). This provision took effect on March 25, 2008.

Review of the safety database for Lusedra (fospropofol disodium) Injection, 35mg/mL, indicated that patients who were in the geriatric age group, or classified as American Society of Anesthesiologists (ASA) III or IV, or weighed less than 60 kg had a higher incidence of hypoxia and airway interventions than the remaining sample population.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of hypoxia and airway intervention in geriatric patients or those classified as ASA Classifications III or IV or patients weighing less than 60 kg treated with Lusedra.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess this signal of a serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct a clinical trial:

5. A dose-ranging clinical trial to evaluate the risk-benefit ratio of Lusedra in patients classified as ASA III or IV, adult patients weighing less than 60 kg, and geriatric patients.

   The timetable you submitted dated December 8, 2008, states that you will conduct this trial according to the following timetable:

Protocol Submission:	by November 2009
Trial Start Date:	by April 2010
Final Report Submission:	by January 2012

Submit the protocols to your IND 62,860, with a cross-reference letter to your NDA 22-244. Submit all final report(s) to your NDA 22-244. Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing study requirements as appropriate:

- **Required Post-marketing Protocol under 505(o)**
- **Required Post-marketing Final Report under 505(o)**
- **Required Post-marketing Correspondence under 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii), provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS

We remind you of your postmarketing study commitment in your communication dated December 11, 2008. This commitment is listed below.

6. A single-dose, open-label, pharmacokinetic trial in breastfeeding women receiving fospropofol for a needed procedure. Concentrations of Lusedra will be assessed in maternal plasma and breast milk so as to estimate potential infant exposure.

Protocol Submission:	by August 1, 2009
Trial Start Date:	by July 1, 2010
Final Report Submission:	by November 1, 2012

Submit the clinical protocol to your IND 62,860 for this product. Submit the study final report to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of the commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and the number of patients entered into the study. All submissions, including supplements, relating to this postmarketing study commitment should be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Allison Meyer, Regulatory Project Manager, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Curt Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures
Package Insert
Carton and Immediate Container labels

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/s/

Curtis Rosebraugh
12/12/2008 05:06:27 PM

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United States Patent and Trademark Office

Patent Bibliographic Data				02/05/2009 03:18 PM	
Patent Number:	6204257		**Application Number:**	09131385	
Issue Date:	03/20/2001		**Filing Date:**	08/07/1998	
Title:	WATER SOLUBLE PRODRUGS OF HINDERED ALCOHOLS				
Status:	12th year fee window opens: 03/20/2012			**Entity:**	Large
Window Opens:	03/20/2012	**Surcharge Date:**	09/21/2012	**Expiration:**	N/A
Fee Amt Due:	Window not open	**Surchg Amt Due:**	Window not open	**Total Amt Due:**	Window not open
Fee Code:	1553	MAINTENANCE FEE DUE AT 11.5 YEARS			
Surcharge Fee Code:					
Most recent events (up to 7):	09/22/2008 08/17/2004	Payment of Maintenance Fee, 8th Year, Large Entity. Payment of Maintenance Fee, 4th Year, Large Entity. --- End of Maintenance History ---			
Address for fee purposes:	BIRCH STEWART KOLASCH & BIRCH PO BOX 747 FALLS CHURCH, VA 220400747				

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United States Patent and Trademark Office

Patent Maintenance Fees		01/29/2009 12:51 PM EST	
Patent Number:	6204257	**Application Number:**	09131385
Issue Date:	03/20/2001	**Filing Date:**	08/07/1998
Window Opens:	03/20/2012	**Surcharge Date:**	09/21/2012
Window Closes:	03/20/2013	**Payment Year:**	
Entity Status:	LARGE		
Customer Number:	000000		
Street Address:	BIRCH STEWART KOLASCH & BIRCH		
City:	FALLS CHURCH		
State:	VA		
Zip Code:	220400747		
Phone Number:	(703) 205-8000		
Currently there are no fees due.			

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BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH VA 22040-0747

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,204,257	**$910.00**	**$0.00**	**08/17/04**	**09/131,385**	**03/20/01**	**08/07/98**	**04**	**NO**	**1257-0116P**

UNITED STATES PATENT AND TRADEMARK OFFICE

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BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH VA 22040-0747

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

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PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,204,257	**$2,360.00**	**$0.00**	**09/22/08**	**09/131,385**	**03/20/01**	**08/07/98**	**08**	**NO**	**JB 9002**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 62,860

Guilford Pharmaceuticals
6611 Tributary Street
Baltimore, MD 21224

Attention: Cathy McDermott, R.N., M.P.H.
Associate Director Regulatory Affairs

Dear Ms. McDermott:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned:	62,860
Sponsor:	Guilford Pharmaceuticals
Name of Drug:	Aquavan™ (propofol) Injection
Date of Submission:	June 28, 2001
Date of Receipt:	June 29, 2001

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, on or before July 29, 2001, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will notify you immediately that (1) clinical studies may not be initiated under this IND ("clinical hold") or that (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have notified you that the information you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170
Attention: Division Document Room, 9B-23
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at 301-827-7410.

Sincerely,

{See appended electronic signature page}

Laura Governale, Pharm.D.
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Laura Governale
7/12/01 03:17:00 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 62,860

Guilford Pharmaceuticals Inc.
6611 Tributary Street
Baltimore, MD 21224

Attention: Louise Peltier
Senior Director, Regulatory Affairs

Dear Ms. Peltier:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Aquavan Injection.

We also refer to your submission dated April 12, 2002, serial number 004, received April 15, 2002, notifying us of your intent to reactivate this IND.

As provided by 21 CFR 312.45(d), studies in humans may not be initiated until 30 days after the date of receipt shown above. If, on or before May 15, 2002, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will notify you immediately that (1) clinical studies may not be initiated under this IND ("clinical hold") or that (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have notified you that the information you submitted is satisfactory.

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, to the following address:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170
Attention: Division Document Room, 9B-23
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at (301) 827-7432.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Kimberly Compton
4/19/02 05:56:38 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-244

NDA ACKNOWLEDGMENT

MGI Pharma
6611 Tributary Street
Baltimore, MD 21224

Attention: Jacqueline Kline, PhD
Director, Regulatory Affairs

Dear Dr. Kline:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: AQUAVAN® (fospropofol disodium) Injection

Date of Application: September 26, 2007

Date of Receipt: September 27, 2007

Our Reference Number: NDA 22-244

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 26, 2007, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

The NDA number provided above shown above be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

If you have any questions, call me, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Allison Meyer
10/15/2007 07:11:48 AM

IND CHRONOLOGY FOR LUSEDRA™

Date of Document	Sub. No.	Sent/ Rec'd	Type	Description
03/19/01		Sent	Meeting Request	Request for Type B Pre-IND Meeting
03/26/01		Received	Acknowledgement	Acknowledgement and scheduled meeting date of May 8, 2001
04/05/01		Sent	Meeting Package	Pre-IND Meeting Package
05/04/01		Sent	Letter	Clarification of Pre-IND Meeting Package
05/14/01		Received	Fax	Request for CMC information
05/31/01		Received	Meeting Minutes	FDA May 8, 2001 Meeting Minutes
06/28/01	000	Sent	IND	Submission of Original IND
07/12/01		Received	Acknowledgement	Acknowledgement of IND 62,860
07/25/01	001	Sent	Response to Request	Response to request for data listing of the toxicokinetic results of the 48 hour monkey study
07/27/01	003	Sent	General Correspondence	Request to inactivate IND
07/27/01	002	Sent	Response to Request	Response to request on the No Observable Effect Level (NOEL) of formate
07/27/01			Meeting Minutes	GPI Meeting Minutes of 7/27/01 teleconference with FDA
08/17/01		Received	Letter & Fax	FDA issues requiring a response prior to activating IND
09/14/01		Received	Fax	FDA clarification of references of 8/17/01 correspondence
01/23/02		Sent	Meeting Request	Request for a Type A Meeting for AQUAVAN™ Injection and inactivated IND 62,860
01/28/02		Sent	Meeting Package	Meeting Package for Type A Meeting
02/28/02		Received	Letter	Type C Meeting scheduled for April 9, 2002

Date of Document	Sub. No.	Sent/ Rec'd	Type	Description
03/14/02		Sent	Letter	Phase I Safety and Tolerability Study Synopsis for discussion at April 9, 2002 meeting with FDA
03/28/02		Sent	General Correspondence	GPI List of Attendees for April 9, 2002 meeting with FDA
04/09/02		Received	Meeting Slides	FDA slides from 4/9/02 meeting with FDA
04/12/02	004	Sent	IND Reactivation	Reactivation of IND 62,860
04/19/02		Received	Letter	Acknowledgement of receipt of notification of intent to reactivate IND
05/22/02		Received	Letter	FDA comments and recommendations and request for information regarding GPI reactivation of IND
05/28/02	005	Sent	Protocol Amendment	Change in Protocol 3000-0206
06/20/02		Received	Meeting Minutes	Meeting Minutes from the April 9, 2002 FDA meeting
07/31/02	006	Sent	Protocol Amendment	Change in Protocol 3000-0206
08/07/02	007	Sent	Protocol Amendment	New Investigator: David Hoelscher, M.D., Austin, Texas (3000-0205)
08/15/02	008	Sent	Response to Request	Response to FDA 5/22/02 letter request for information
08/16/02	009	Sent	Information Amendment	Final Pharmacology/Toxicology reports
08/19/02	010	Sent	Information Amendment	Final Pharmacology/Toxicology reports
08/20/02	011	Sent	Information Amendment	Final Pharmacology/Toxicology reports
09/24/02	012	Sent	Information Amendment	Response to Important Points and Action Items from 4/20/02 Meeting Minutes
10/02/02	013	Sent	Information Amendment	Update on Pharm/Tox reports and request for FDA input on proposed new protocol 3000-0207
11/04/02	014	Sent	Information Amendment	Toxicology Final Reports: GPI 3000-15715-00-02N and GPI 3000-15715-00-06G
11/05/02	015	Sent	Information Amendment	Toxicology Final Reports: GPI 3000-15715-00-01N and GPI 3000-15715-01-02G

Date of Document	Sub. No.	Sent/ Rec'd	Type	Description
01/24/03	016	Sent	Protocol Amendment	New Investigator: Dr. Ronald Pruitt, Nashville, TN (Protocol 3000-0207)
01/27/03	017	Sent	Protocol Amendment	New Investigator: Dr. Aziz Laurent, Austin, TX; (Protocol 3000-0206)
01/31/03	018	Sent	Protocol Amendment	New Investigator: Dr. Howard Schwartz, Miami, FL (Protocol 3000-0207)
02/24/03	019	Sent	Protocol Amendment	New Protocol: 3000-0207 "A Phase 2, Two Part Study of AQUAVAN™ Injection In the Presence of Pre-Medication in Patients Undergoing Elective Colonoscopy"
02/26/03	020	Sent	Protocol Amendment	New Investigator: Dr. Michael Weinstein, Chevy Chase, MD (Protocol 3000-0207)
06/13/03	021	Sent	Meeting Request	Request for Type C Meeting for AQUAVAN® Injection
06/27/03	023	Sent	Protocol Amendment	Change in protocol 3000-0207
06/27/03	022	Sent	Protocol Amendment	New Investigator: Dr. Andrew Catanzaro, Detroit, MI (Protocol 3000-0207)
07/15/03	026	Sent	Meeting Request	Request for Type C Meeting to discuss current revised clinical development plan
07/15/03	025	Sent	Protocol Amendment	New Protocol: A Phase I, Open Label, Safety and Tolerability Study of AQUAVAN® Injection in Healthy Volunteers Pre-Medicated with Lidocaine HCI Injection (3000-0308)
07/23/03	027	Sent	Annual Report	Period: May 22, 2002 – May 21, 2003
07/30/03		Received	Letter	FDA's decision to have one meeting and to incorporate questions into the meeting currently scheduled for August 27, 2003
08/15/03	028	Sent	Meeting Package	Meeting Package for August 27, 2003 meeting with FDA
08/21/03	029	Sent	Protocol Amendment	New Investigator: Dr. Aziz Laurent, Austin, TX (3000-0308)
08/26/03	030	Sent	General Correspondence	Meeting Package corrections
08/27/03		Received	Meeting Slides	FDA Meeting Slides from August 27, 2003 meeting
09/25/03	031	Sent	Protocol Amendment	New Investigator: Dr. Jeffrey Medoff, Greensboro, NC; Dennis Riff, Anaheim, CA (3000-0207)

Date of Document	Sub. No.	Sent/ Rec'd	Type	Description
09/30/03		Received	Meeting Minutes	FDA August 27, 2003 Meeting Minutes
10/10/03	032	Sent	Protocol Amendment	New Investigator: Lawrence Cohen, New York, NY (3000-0207)
11/18/03	033	Sent	Protocol Amendment	Change in Protocol 3000-0207
12/05/03	034	Sent	General Correspondence	Request for a Conference Call
12/17/03	035	Sent	General Correspondence	Follow-up to request for a conference call
12/19/03	036	Sent	Meeting Request	Request for Type B End of Phase II Meeting
12/22/03	037	Sent	General Correspondence	Withdraw of 12/5/03 request for a conference call
02/06/04		Received	Acknowledgement	Acknowledgement of FDA scheduled meeting for March 31, 2004
03/02/04	038	Sent	Meeting Package	Meeting Package for March 31, 2004 FDA meeting
03/24/04	039	Sent	General Correspondence	Additional question or the Division and a clarification regarding dosing of Midazolam HCl
03/31/04	040	Sent	Information Amendment	Final toxicology report for study 3000-15717-03-01G
03/31/04			Meeting Minutes	GPI March 31, 2004 Meeting Minutes
04/02/04		Received	Fax	FDA fax with copy of slides from 3/31/04 FDA meeting
04/29/04	041	Sent	Information Amendment	Final toxicology report for study 1707-007
04/30/04		Received	Meeting Minutes	FDA March 31, 2004 Meeting Minutes
05/12/04	042	Sent	Protocol Amendment	New Protocol No. 3000-0410, A Phase III, Randomized, Open-Label Study to Assess the Safety and Efficacy of AQUAVAN® Injection Versus Midazolam HCL for Sedation in Patients Undergoing Colonoscopy Procedures
05/17/04	043	Sent	General Correspondence	Appropriately identifying Protocol Amendment (Serial No. 042) as a "Phase III, Pivotal Design Colonoscopy Trial"

Date of Document	Sub. No.	Sent/ Rec'd	Type	Description
05/26/04	044	Sent	General Correspondence	Addendum to March 31, 2004 Meeting Minutes
06/16/04			Phone Contact	Memo – Note to File: Messages left with Kim Compton, FDA Project Manger
06/18/04			Phone Contact	Memo – Note to File: Phone Conversation with Kim Compton, FDA Project Manger
07/02/04	045	Sent	Information Amendment	Request for confirmation that preclinical studies support proposed labeling
07/08/04		Received	Fax	Slides from a presentation by Dr. Meyer
07/15/04	046	Sent	Information Amendment	Final toxicology report for study 4113612, June 30, 2004
07/16/04		Received	Telecon Minutes	FDA 6/23/04 telecon minutes
07/16/04		Received	Request for Information	FDA request for information following their clinical review
07/26/04	047	Sent	Response to Request	Response to FDA request and revised Phase 3 clinical program
07/28/04		Sent	Phone Contact	Telephone conversation regarding proposed trademark for AQUAVAN
07/30/04	048	Sent	General Correspondence	GPI's intent to initiate colonoscopy study while designing the new study
07/30/04			Phone Contact	Consideration for Guilford's proposed Phase 3 colonoscopy protocol
08/03/04	049	Sent	Information Amendment	Toxicology reports: 411198, 1707-006, and WIL-458007
08/04/04			Phone Contact	Follow-up to July 30 submission: Consideration for Guilford's proposed Phase 3 Colonoscopy protocol
08/06/04	051	Sent	General Correspondence	Questions to be discussed during the upcoming 8/11/04 teleconference
08/06/04	050	Sent	Annual Report	Period: May 22, 2003 to May 21, 2004
08/09/04	052	Sent	Protocol Amendment	New Protocol: 3000-0409: A Phase III, Randomized, Open-Label Study To Assess The Safety And Efficacy Of AQUAVAN® Injection Versus Midazolam HCl For Sedation In Patients Undergoing Flexible Bronchoscopy Procedures
08/10/04		Received	E-mail	FDA comments to discuss at 8/11/04 teleconference

Date of Document	Sub. No.	Sent/ Rec'd	Type	Description
08/12/04	053	Sent	Protocol Amendment	Change in Protocol 3000-0410
08/13/04	054	Sent	General Correspondence	List of 8/11/04 teleconference attendees and thank you
08/17/04	055	Sent	Information Amendment	Revised Investigator's Brochure, August 16, 2004
08/25/04	057	Sent	General Correspondence	GPI August 11, 2004 FDA teleconference minutes
08/25/04	056	Sent	Information Amendment	Toxicology reports GPI 3000-15715-01-01N and GPI 3000-15715-02-02N
08/26/04	058	Sent	Protocol Amendment	New Protocol 3000-0412 – Minor Surgical Procedures
09/03/04	060	Sent	Protocol Amendment	New protocol 3000-0411 – Percutaneous Coronary Procedures
09/03/04	059	Sent	Protocol Amendment	New Investigators (Protocol 3000-0410): M. Weinstein (Chevy Chase, MD), C. Barish (Raleigh, NC), BR Bhandari (Monroe, LA), D. Pambianco (Charlottesville, VA), H. Tatum (Tulsa, OK), C.A. Goetsch (Huntsville, AL), D. Maccini (Spokane, WA) and B. Saltzberg (Atlanta, GA)
09/10/04	061	Sent	Information Amendment	Statistical Analysis Plan – 3000-0410
09/14/04		Sent	Request for Desk Copy	Desk Copy of Serial No. 045 for Allison Meyer
09/14/04		Received	Meeting Minutes	FDA 8/11/04 Meeting Minutes
09/27/04	062	Sent	Protocol Amendment	Protocol Amendment 3000-0409 – Bronchoscopy Procedures
09/29/04	064	Sent	Protocol Amendment	New Investigator (3000-0409): James Hansbrough (Bowling Green, KY)
09/29/04	063	Sent	Protocol Amendment	New Investigator (3000-0410): Ronald Pruitt (Nashville, TN)
10/01/04	065	Sent	Information Amendment	Statistical Analysis Plan for protocol 3000-0409
10/05/04	067	Sent	Protocol Amendment	New Investigators (3000-0410): L. Cohen (NY), B. Winston (TX)
10/05/04	066	Sent	Protocol Amendment	New Investigators (3000-0409): E. Diamond (IL), D. Handshoe (SC), K Popovich (MT), Gotfried (AZ)

Date of Document	Sub. No.	Sent/ Rec'd	Type	Description
10/20/04		Sent	General Correspondence	GPI certification that electronic signatures using validated systems for regulated operations are equivalent of traditional handwritten signatures
10/20/04			Phone Contact	Telecon notes with Dr. Jeremy Ruskin
10/25/04	068	Sent	Protocol Amendment	New Investigators: (3000-0409) - Michael G. Milam, M.D, Lynchburg, VA; Daniel E. Ray, M.D, Allentown, PA; Donald L. DeCoy, M.D, High Point, NC; Edward Frank Fara, M.D., Munster, IN; (3000-0412) - Bradley A. Barter, D.O., State College, PA; Eric L. Diamond, D.P.M., Owings Mills, MD; David L. Fox, M.D., San Antonio, TX; Michael J. Curtin, M.D, Boise, ID
10/26/04	069	Sent	Information Amendment	Transfer of obligations to PPD for the Bronchoscopy study 3000-0409 and the Colonoscopy study 3000-0410
10/29/04			Phone Contact	Status of 7/2/04 Pharm/Tox submission, Serial No. 045
11/01/04	070	Sent	Information Amendment	Statistical Analysis Plan for Protocol 3000-0412
11/12/04		Sent	Email	Email regarding status of pharm/tox review
11/22/04	071	Sent	Meeting Request	Request for Type C Meeting
11/23/04	072	Sent	General Correspondence	Statistical questions for future NDA filing
11/24/04	073	Sent	Protocol Amendment	New Protocol 3000-0419 (A Phase III Pilot, Randomized, Placebo-controlled, Double-Blind Study to Assess the Efficacy and Safety of Procedural Sedation with AQUAVAN® Injection in Patients Undergoing Colonoscopy)
11/24/04		Sent		Additional copies of Information Amendment submitted July 2, 2004, Serial No. 045, as requested
11/24/04		Received	Phone Contact	Request for additional copies of Serial No. 045
11/30/04		Received	Letter	Requested meeting scheduled for February 2, 2004
12/02/04	074	Sent	Protocol Amendment	New Investigators: Protocol 3000-0409: Thomas DeMartini, M.D., Decatur, GA; Keith Harless, M.D., Bend, OR; Charles Andrews, M.D., San Antonio, TX; Wilson Smith, Jr., M.D., Spartanburg, SC; Praveen Mathur, M.D., Indianapolis, IN; John Beamis, Jr., M.D., Burlington, MA.

Date of Document	Sub. No.	Sent/ Rec'd	Type	Description
				Protocol 3000-0410: Joseph Geenen, M,D,m Milwaukee, WI 53215. Protocol 3000-0411: Robert Weiss, M.D., Auburn, ME. Protocol 3000-0412: William Jennings, M.D., San Antonio, TX; John Burrell, M.D., Layton, UT; Arthur Tallis, M.D., Phoenix, AZ; Joseph Grillo, M.D., Oklahoma City, OK
12/08/04	075	Sent	Information Amendment	Revised Statistical Analysis Plan for Protocol 3000-0410 and new Statistical Analysis Plan for Protocol 3000-0411
12/10/04	076	Sent	General Correspondence	Request for Type C Meeting
12/13/04		Received	Phone Contact	FDA rejected meeting request, but rather to meet internally in January and provide GPI with written comments
12/14/04		Sent	Phone Contact	GPI request for FDA to reconsider Type C meeting request
12/15/04		Received	Letter	FDA formal meeting rejection, but will provide written comments on protocol 3000-0419
12/16/04	077	Sent	Protocol Amendment	New Protocols: 3000-0416 entitled "A Phase II Open-Label Study to Assess the Safety and Efficacy of AQUAVAN® Injection for Sedation in Patients with End Stage Renal Disease Undergoing Vascular Access Procedures." 3000-0417 entitled "A Phase II Open-Label Study to Assess the Safety and Efficacy of AQUAVAN® Injection for Sedation in Patients with Hepatic Impairment Undergoing Esophagogastroduodenoscopy (EGD)"
12/17/04	078	Sent	Information Amendment	Transfer of obligations to PPD for protocols 3000-0412 – Minor Surgical Procedures, 3000-0416 – Vascular Access Procedures, and 3000-0417 - Esophagogastroduodenoscopy (EGD)
12/20/04	079	Sent	Protocol Amendment	New Investigators: Protocol 3000-0409: A. Seibert, MD, Mobile, AL. Protocol 3000-0410: M. Eisner, MD, Zephyrhills, FL, B. Long, MD, Jackson, MS, B. Overhold, MD, Knoxville, TN, D. Stanton, MD, Orange, CA, I. Stein, MD, Nashville, TN, M Koch, MD, Silver Spring, MD. Protocol 3000-0411: J Griffin, MD, Virginia Beach, VA. Protocol 3000-0412: M. Jove, MD, Decatur, GA, J Barnes, MD, Portland, OR, D. Farrell MD, McCook, NE, I Gotlieb, MD, Pasadena, MD
12/22/04	080	Sent	Protocol Amendment	New Protocol 3000-0415 Elderly Colonoscopy. Change in Protocol 3000-0409 Bronchoscopy and 3000-0411 Cardiac

Date of Document	Sub. No.	Sent/ Rec'd	Type	Description
01/10/05	081	Sent	Information Amendment	Transfer of obligations to PPD for protocol 3000-0415 – Elderly Colo.
01/14/05	082	Sent	Information Amendment	Final Clinical Study Report 3000-0205
01/20/05	083	Sent	Protocol Amendment	Change in Protocol 3000-0419
01/28/05	084	Sent	Protocol Amendment/ Information Amendment	New Protocol 3000-0413 – ICU and Transfer of Obligations to PPD for Protocol 3000-0413
01/31/05	085	Sent	Protocol Amendment	New Investigators; Protocol 3000-0409: Ron J. Kattoo, M.D., Detroit, MI; 3000-0411: John Sunew, M.D., Alexandria, VA, Rackesha Pradshad, M.D., Ocala, FL; 3000-0412: Scott Crampton, MD, Bullhead City, AZ, Hassan Hammoud, MD, Dearborn, MI, Paul Diehl, M.D., Sandy, UT, William Donahue, Jr, M.D., Cleveland, OH, Michael Ellerbusch, M.D., Northport, AL, Joseph Gimbel, MD, Phoenix, AZ, M. Jay Jazayeri, M.D., Long Beach, CA, Glynne Stanley, MB.ChB.FRCA, Boston, MA, Dilip Tapadiya, MD, Fountain Valley, CA. Stuart Phillips, MD, Phoenix, AZ; 3000-0415: Bruce Salzberg, MD, Atlanta, GA, Mark Eisner, MD, Zephyrhills, FL
02/01/05		Received	Phone Contact	FDA will prepare a statement and telecom will not be necessary. FDA email response to Serial No. 045 preclinical request
02/03/05	086	Sent	Information Amendment	Pharmacokinetic report 04-GUIL.P01R1 & 4GUILP8
02/10/05	087	Sent	Information Amendment	Final Toxicology Report: 3000-15715-02-01G (01-3489)
02/18/05	089	Sent	Protocol Amendment	Change in protocols 3000-0409, 3000-0411, and 3000-0412
02/18/05	088	Sent	Protocol Amendment	New protocol 3000-0418-Burn and transfer of obligations to PPD
02/23/05		Received	Phone Contact	Status of placebo colonoscopy protocol review and the eCTD
02/28/05	090	Sent	Protocol Amendment	New Investigators: Protocol 3000-0409: Austin B. Thompson, III, M.D., Omaha, NE; Patrick E. Whitten, M.D., Peoria, IL; Curtis N. Sessler, M.D., Richmond, VA; Devendra Natverlal Amin, M.D., Clearwater, FL; Charlton Strange, M.D., Charleston, SC; Emory H. Robinette, M.D., Abingdon, VA; Protocol 3000-0411: Bruce E. Murphy, M.D., Little Rock, AR; Kishor Vora, M.D., Owensboro, KY; Mark Reisman, M.D., Seattle, WA; Protocol 3000-0412: Richard Sellers, M.D., Pensacola, FL; William Lipman, M.D., Salisbury, MA; Bernard N. Stulberg, M.D., Cleveland, OH; Ralph A. Liebelt, M.D., Durham, NC; Protocol 3000-0415: Michael L. Weinstein, M.D., Chevy Chase,

Date of Document	Sub. No.	Sent/ Rec'd	Type	Description
				MD; Lawrence B. Cohen, M.D., New York, NY; David M. Maccini, M.D.; Spokane, WA; Daniel John Pambianco, M.D., Charlottesville, VA; Bal Raj Bhandari, M.D., Monroe, LA; C. Allen Goetsch, M.D., Huntsville, AL; Barry Winston, M.D., Houston, TX; Joseph E. Geenen, M.D., Milwaukee, WI; Billy Wayne Long, M.D., Jackson, MS; Bergein F. Overholt, M.D., Knoxville, MD; Ira Edward Stein, M.D., Nashville, TN; Milton J. Koch, M.D., Silver Spring, MD; David Silvers, M.D., Metairie, LA; Lawrence D. Wruble, M.D., Memphis, TN; Protocol 3000-0416: Maciej L. Dryjski, M.D., Buffalo, NY
03/01/05		Sent	Protocol	Protocol 3000-0417 – hepatic, as requested
03/01/05		Received	Email	Request for Desk Copy of hepatic protocol, 3000-0417
03/03/05	091	Sent	Information Amendment	Revised 3000-0410 Statistical Analysis Plan
03/17/05		Sent	Safety Report	Fax of SAE 05USA0081(0) sent by Dr. Bray
03/18/05	092	Sent	Meeting Request	Request for Type A Meeting
03/21/05		Received	Phone Contact	FDA request for a teleconference regarding the 7-Day Alert, however GPI's meeting request had addressed their concerns and that the meeting is scheduled for April 11, 2005 at 4:00 p.m.
03/22/05	093	Sent	IND Safety Report	Initial Written Report for 05USA0081(0)
03/23/05		Received	Acknowledgement	Acknowledgement of receipt of our meeting request and scheduling of the meeting for April 11, 2005 at 4:00 p.m.
03/28/05		Sent	Email	Email regarding the 4/11/05 Meeting Package
03/28/05	094	Sent	Meeting Package	April 11, 2005 Meeting Package, Vol. 1 (Question 1) and Vol. 2 (Questions 2-5)
03/29/05	095	Sent	General Correspondence	Signed FDA Form 1571 for Serial No. 094
03/29/05		Sent	Email	GPI questions regarding Serial No. 094 and FDA's response
04/01/05	096	Sent	Protocol Amendment	New Investigators: Protocol 3000-0409: Shawn E. Wright, M.D., Phoenix, AZ; Richard M. Kahn, M.D., Auburn, ME; Protocol 3000-0410: Jeffrey Roy Medoff, M.D., Greensboro, NC; James S. Novick, M.D., Towson, MD; Protocol 3000-0411: Jay

Date of Document	Sub. No.	Sent/ Rec'd	Type	Description
				Kantilal Patel, M.D., Hamilton, NJ; Jay Clyde Koons, M.D., Gainesville, FL; Protocol 3000-0412: Jeffrey C. Davis, M.D., Birmingham, AL; Protocol 3000-0417: Thomas Dominic Schiano, M.D., New York, NY; Protocol 3000-0419: Michael L. Weinstein, M.D., Chevy Chase, MD; C. Allen Goetsch, M.D., Huntsville, AL; Mark Eisner, M.D., Zephyrhills, FL
04/05/05	098	Sent	Information Amendment	Toxicology Report GPI 15715-TOX-04-007 (Single Dose Study in Rabbits)
04/05/05	097	Sent	Information Amendment	Transfer of obligations to PPD for Protocol 3000-0411-Cardiac
04/08/05	099	Sent	General Correspondence	List of GPI attendees for April 11, 2005 Meeting with FDA
04/11/05		Received	FDA Slides	FDA slides from the 4/11/05 FDA meeting
04/14/05	100	Sent	Information Amendment	Withdraw of protocol 3000-0419
04/15/05	101	Sent	Protocol Amendment	Change in Protocol 3000-0414 (Original protocol 3/24/05 included; no patients enrolled)
04/21/05	102	Sent	General Correspondence	Exclusion of clinical data from R. Pruitt, protocol 3000-0410 and closure of clinical site
04/25/05	103	Sent	Protocol Amendment Information Amendment	New Protocol 3000-0520 – Dose response in Colonoscopy, as well as the additional information on PK/PD model, and the withdraw of protocols 3000-0416, 3000-0417, and 3000-0418
04/28/05	104	Sent	Information Amendment	Modified Clinical Development Plan and GPI 4/11/05 Meeting Minutes
05/11/05		Received	Meeting Minutes	FDA Meeting Minutes from April 11, 2005 Meeting
05/11/05		Sent	Phone Contact	Status of April 11, 2005 Type A meeting minutes, comments on Dose Response trial 0520, comments on revised Clinical Development Program
05/11/05	105	Sent	Protocol Amendment	Change in Protocol 3000-0414
05/26/05		Received	Email	Status of Dose-controlled study (3000-0520) submitted 4/25/05
06/01/05	106	Sent	Protocol Amendment	New Investigator: Protocol 3000-0413 - Robert Brewer, M.D., Detroit, MI; Protocol 3000-0414 - D. Ronald Goldwater, M.D., Baltimore, MD

Date of Document	Sub. No.	Sent/ Rec'd	Type	Description
06/03/05	107	Sent	Information Amendment	Toxicology Protocol: L5178Y TK +/- Mouse Lymphoma Forward Mutation with GPI 15715 (AQUAVAN): Formaldehyde Effects (6778-161) Expert Report: Genotoxicity of GPI 15715 (AQUAVAN), An Assessment Toxicology Reports: Single Dose Toxicity/Irritation Study With GPI 15715 By Subcutaneous Dosing in Sprague Dawley Rats (NOTOX Project 411323) Effects of GPI 15715 (AQUAVAN®), Propofol (Diprivan®) and Propofolk (Di-isoproply phenol) on Cloned hERG Channels Expressed in Mammialian Cells (ChanTest Study Number 041112.HQL- GPI-15715-TOX-04-019) Effects of GPI 15715 (AQUAVAN®) and Propofol on Action Potentials in Isolated Canine Cardiac Purkinje Fibers (ChanTest Study Number 041113.HQL - GPI -15715-TOX-04-020)
06/20/05		Sent	Response to Request	Response to request for a Desk Copy of Submission 103
06/20/05		Received	Email	Email updating GPI that the dose response protocol (3000-0520) is going through secondary review. FDA also requested a desk copy of submission 103
06/21/05	108	Sent	General Correspondence	Request for FDA comments on Phase 3 Protocol: Dose Response Study in Colonoscopy patients (3000-0520)
06/24/05	109	Sent	Annual Report	Period: May 22, 2004 – March 28, 2005
06/28/05	111	Sent	Protocol Amendment	Change in Protocol: 3000-0414 - A Phase 1 Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Drug Interaction Study of AQUAVAN® Injection and Premedications in Healthy, Adult Subjects
06/28/05	110	Sent	Protocol Amendment	New Protocol: 3000-0521 - A Single-Site, Randomized, 4-Sequence, 4-Treatment Crossover Study of a Single Administration of AQUAVAN Injection Compared with Placebo and a Positive Control in Healthy Volunteers
06/30/05	113	Sent	Protocol Amendment	New Investigator: Protocol 3000-0413: Dr. Sam Sum-Ping, Dallas TX, and Dr. Ruben Azocar, Boston, MA
06/30/05	112	Sent	Information Amendment	Notification to FDA that protocols 3000-0409 (Bronchoscopy), 3000-0411 (Cardiac), and 3000-0412 (Minor Surgery) were stopped in March, 2005, due to a change in the dosing regimens, as discussed with FDA

Date of Document	Sub. No.	Sent/ Rec'd	Type	Description
07/06/05		Sent	Email	Frank Sasinowski (Hyman, Phelps & McNamara) email to Bob Rapport regarding the status of protocol 3000-0520
07/13/05		Sent	Fax & Email	Permission for Frank Sasinowski to discuss the AQUAVAN clinical development program with FDA
07/15/05		Sent	Email	Status of dose-response protocol. (3000-0520)
07/20/05		Received	Email Response	FDA response to dose-response protocol (3000-0520), submitted 4/25/05 (Serial No. 103) with comments and recommendations
07/25/05	114	Sent	Protocol Amendment	New Protocol 3000-0520 – Dose response in Colonoscopy
07/28/05	115	Sent	Information Amendment	CMC Update
08/01/05	116	Sent	Protocol Amendment	New Investigators (3000-0413): Jane Fitch, Oklahoma City, OK; (3000-0520): Michael L. Weinstein, Chevy Chase, MD; Bruce Salzberg, Atlanta, GA
08/02/05	118	Sent	IND Safety Report	Initial and follow-up safety report 05USA0150(0) and 05USA0150(1)
08/02/05	117	Sent	Information Amendment	Transfer of Obligations for Protocol 3000-0414 to PAREXEL
08/03/05	119	Sent	Information Amendment	New Statistical Analysis Plans for 3000-0413, 3000-0415, 3000-0520 (Volume 1); revised Statistical Analysis 3000-0409, 3000-0411, 3000-0412 (Volume 2)
08/22/05	120	Sent	Protocol Amendment	Protocol Amendments 1 and 2 for Protocol 3000-0413-ICU
08/31/05	121	Sent	Protocol Amendment	New Investigators: Protocol 3000-0413: Christopher Young, M.D., Durham, NC; Alex Y, Bekker, M.D.,New York, NY; G. Bruce Waldon, M.D., Rogers, AR; Protocol 3000-0520: Lawrence B. Cohen, M.D., New York, NY; David M. Maccini, M.D., Spokane, WA; Bal Raj Bhandari, M.D., Monroe, LA; C. Allen Goetsch, M.D., Huntsville, AL; Harvey A. Tatum, M.D., Tulsa, OK; Joseph E. Geenen, M.D., Milwaukee, WI; Billy W. Long, M.D., Jackson, MS; Lawrence D. Wruble, M.D., Memphis, TN; Bruce Schneider, M.D., Mark Noar, M.D., Towson, MD; Antonio Granda, M.D., Nashville, TN; Eric Lawitz, M.D., San Antonio, TX; Shaban Faruqui, M.D., Baton Rouge, LA; John F. Johanson, M.D., Rockford, IL
09/14/05	122	Sent	Protocol Amendment	New Statistical Analysis Plan for 3000-0414 – Drug Interaction

Date of Document	Sub. No.	Sent/ Rec'd	Type	Description
09/30/05	123	Sent	Protocol Amendment	New Investigators: Protocol 3000-0413: Richard Kahn, M.D., Auburn, ME; Philip Lebowitz, M.D., Bronx, NY; Anthony Manasia, M.D., New York, NY; Protocol 3000-0520 : Ira E. Stein, M.D., Nashville, TN; Mark Noar, M.D., Towson, MD; Shaban Faruqui, M.D., Baton Rouge, LA; Joseph Greco, M.D.; Mineola, NY; William Robert Harlan, III, M.D., Asheville, NC; Protocol 3000-0521: Thomas L. Hunt, M.D., Austin, T.
10/03/05	124	Sent	Letter	Transfer of Ownership to MGI PHARMA
10/11/05	125	Sent	Protocol Amendment	Change in Protocol: 3000-0521 - A Single-Site, Randomized, 4-Sequence, 4-Treatment Crossover Study of a Single Administration of AQUAVAN Injection Compared with Placebo and a Positive Control in Healthy Volunteers
10/14/05	126	Sent	Protocol Amendment	New Protocol 3000-0522: A Phase 3, Randomized, Double-blind, Dose-Controlled Study to Assess the Efficacy and Safety of AQUAVAN® (fospropofol disodium) Injection for Minimal-to-Moderate Sedation in Patients Undergoing Colonoscopy
10/21/05	127	Sent	Information Amendment	Toxicology Reports: GPI 15715-05-031 (Eye Irritation-Rabbits), GPI 15715-05-032 (Skin Irritation-Rabbits), GPI 15715-05-033 (Dermal Sensitization-Guinea Pigs)
11/29/05	128	Sent	Protocol Amendment	New Protocol 3000-0523: A Phase 3, Open-Label, Single Arm Study to Assess the Safety of AQUAVAN® (fospropofol disodium) Injection for Minimal-to-Moderate Sedation in Patients Undergoing Minor Surgical Procedures New Protocol 3000-0524: A Phase 3, Randomized, Double-Blind, Dose-Controlled Study to Assess the Efficacy and Safety of AQUAVAN® (fospropofol disodium) Injection for Minimal-to-Moderate Sedation in Patients Undergoing Flexible Bronchoscopy
12/05/05	129	Sent	Information Amendment	Revised SAP for Protocol 3000-0520 – Dose response in Colonoscopy
12/07/05	130	Sent	Protocol Amendment	New Investigator – Protocol 3000-0413: Cordelia Sharma, M.D., NY; Keith Candiotti, M.D., Miami, FL
01/03/06	132	Sent	Protocol Amendment	New Investigator – Protocol 3000-0522: Lawrence B. Cohen, M.D., New York, NY; Michael F. Kestell, M.D., Spokane, WA; Atul Shah, M.D., Prince Frederick, MD; Jack R. Groover, M.D., Jacksonville, FL; John Weber, M.D., Troy, MI
01/03/06	131	Sent	Information Amendment	Statistical Analysis Plan for 3000-0521

Date of Document	Sub. No.	Sent/ Rec'd	Type	Description
01/24/06	133	Sent	Information Amendment	Airway Interventions Update provided as agreed
02/20/06	134	Sent	Protocol Amendment	Change in Protocol 3000-0413: A Phase II, Randomized, Open-Label Study to Examine the Safety and Efficacy of AQUAVAN® Injection for Sedation of Patients Requiring Intubation and Mechanical Ventilation in the Intensive Care Unit Setting
02/22/06	135	Sent	Protocol Amendment	Change in Protocol 3000-0522: A Phase 3, Randomized, Double-Blind, Dose-Controlled Study to Assess the Efficacy and Safety of AQUAVAN® (Fospropofol Disodium) Injection for Minimal-to-Moderate Sedation in Patients Undergoing Colonoscopy
02/28/06	136	Sent	Protocol Amendment	New Investigator – Protocol 3000-0413: John V. White, M.D.
03/14/06	137	Sent	Protocol Amendment	Change in Protocol 3000-0524: 0.A Phase 3, Randomized, Double-Blind, Dose-Controlled Study to Assess the Efficacy and Safety of AQUAVAN® (fospropofol disodium) Injection for Minimal-to-Moderate Sedation in Patients Undergoing Flexible Bronchoscopy
03/17/06	138	Sent	Information Amendment	3000-0522 Statistical Analysis Plan: A Phase 3, Randomized, Double-Blind, Dose-Controlled Study to Assess the Efficacy and Safety of AQUAVAN® (Fospropofol Disodium) Injection for Minimal-to-Moderate Sedation in Patients Undergoing Colonoscopy
03/31/06	139	Sent	Protocol Amendment	New Investigator – Protocol 3000-0413: Pamela R. Roberts, M.D. Protocol 3000-0522: C. Allen Goetsch, M.D., Eric Lawitz, M.D., John F. Johanson, M.D., William R. Harlan, M.D., Edward L. Cattau, M.D.
04/03/06		Received	Letter	FDA comments and recommendations regarding protocol 3000-0521, A Single-Site, Randomized, 4-Sequence, 4-Treatment Crossover Study of a Single Administration of AQUAVAN Injection Compared with Placebo and a Positive Control in Healthy Volunteers
04/05/06	0140	Sent	Information Amendment	Toxicology report GPI 15715-TOX-04-022, entitled "L5178y $TK^{+/-}$ Mouse Lymphoma Forward Mutation Assay with GPI 15715 (AQUAVAN®): Formaldehyde Effects"
04/13/06	0142	Sent	Information Amendment	Clinical: Airway Interventions Update #2
04/13/06	0141	Sent	Information Amendment	Transfer of obligations for Protocol 3000-0521 to PPD Development, LP, The Total

Date of Document	Sub. No.	Sent/ Rec'd	Type	Description
				Approach, and eResearch Technology, Inc.
04/20/06	0143	Sent	Protocol Amendment	Change in Protocol 3000-0523: A Phase 3, Open-Label, Single Arm Study to Assess the Safety of AQUAVAN® (fospropofol disodium) Injection for Minimal-to-Moderate Sedation in Patients Undergoing Minor Surgical Procedures
04/28/06	0144	Sent	Protocol Amendment	New Investigator- Protocol 3000-0413:James Berry, M.D, Jeffrey Littman, M.D.,Kent Pearson, M.D. Protocol 3000-0522: Richard M. Chasen, M.D., Joseph E. Geenen, M.D.,Billy Wayne Long, M.D., Rodger Sleven, M.D., Ira E. Stein, M.D., Michael L. Weinstein, M.D. Protocol 3000-0524: Emory Robinette, M.D.
05/01/06	0145	Sent	Information Amendment	Statistical Analysis Plan (SAP): 3000-0524 A Phase 3, Randomized, Double-Blind, Dose-Controlled Study to Assess the Efficacy and Safety of AQUAVAN® (fospropofol disodium) Injection for Minimal-to-Moderate Sedation in Patients Undergoing Flexible Bronchoscopy
05/15/06	0146	Sent	Protocol Amendment	New Investigator-Protocol 3000-0524: Richard Kahn, M.D.
05/19/06	0147	Sent	Letter	Study 3000-0520-Request to Review SDTM Sample Submission 900208 with CD
05/31/06	0148	Sent	Protocol Amendment	New Investigator-Protocol 3000-0413: David L. Bowton, M.D.,Protocol 3000-0522 Investigator revisions and Protocol 3000-0524: Carmel Joesph, M.D., Piyush Patel, M.D. and David Phillips, M.D.
06/07/06	0149	Sent	Annual Report	Period March 29, 2005 – March 28, 2006
06/09/06	0150	Sent	Information Amendment	Clinical-Transfer of Obligations for Protocol 3000-0524 to Pharmaceutical Research Associates, Inc. (PRA)
06/19/06	0152	Sent	Information Amendment	Statistical Analysis Plan (SAP): 3000-0523 A Phase 3, Open-Label, Single Arm Study to Assess the Safety of AQUAVAN® (fospropofol disodium) Injection for Minimal-to-Moderate Sedation in Patients Undergoing Minor Surgical Procedures
06/19/06	0151	Sent	Protocol Amendment	New Protocol 3000-0625: A Phase 1, Open Label, Single Dose, Cross-Over Pharmacokinetic/Pharmacodynamic Study of AQUAVAN® (fospropofol disodium) Injection Versus Diprivan® Injectable Emulsion in Volunteers
06/20/06		Received	Email	Email from FDA regarding SDTM Sample Data Sets-900208

Date of Document	Sub. No.	Sent/ Rec'd	Type	Description
06/30/06	0153	Sent	Protocol Amendment	New Investigator-Protocol 3000-0522:Douglas Reg, M.D.,Bruce Schneider, M.D.,Harry Wasvary, M.D., Protocol 3000-0523: Evan R. Goldfischer, M.D.,Ira J. Gottlieb, D.P.M., Protocol 3000-0524: David Handshoe, M.D.
07/19/06		Received	Phone Contact	Phone Request regarding 3000-0524 for the Aquavan Medical Reviewer
07/25/06	0154	Sent	Response to Request	Response to a Request from FDA-in reference to Study 3000-0524
07/25/06		Sent	Email	Response to Request for Information from FDA in reference to Study 3000-0524
07/25/06		Sent	Email	Additional Information on Study 3000-0524-Reduction in doses
07/31/06	0155	Sent	Protocol Amendment	New Investigator-Protocol 3000-0522:Joseph E. Geenen, M.D.,Michael F. Kestell, M.D., Muhammad Y. Sheikh, M.D.,John Weber, M.D., Protocol 3000-0523: Bradley Berry, M.D., Vasanth K. Bethala, M.D.,Evan Ekman, M.D., Ira J. Gottlieb, D.P.M., Protocol 3000-0524: James M. Fuller, M.D., James Hansbrough, M.D., Boris Murillo, M.D., Allan Seibert, M.D., Richard Sellman, M.D. and Gerard Silvestri, M.D.
08/03/06	0156	Sent	Information Amendment	Clinical Update-Airway Interventions-2nd Quarter, 2006
08/08/06	0157	Sent	Response to Request	QTc Response to comments and Recommendations
08/08/06		Received	Email	Response to Request for information regarding Study 3000-0524
08/10/06	0158	Sent	Response to Request	Response to Request for information regarding Study 3000-0524
08/17/06		Received	Phone Contact	Phone request for a telecom regarding Study 3000-0524
08/25/06	0159	Sent	Information Amendment	Clinical-3000-0522 Statistical Analysis Plan: A Phase 3, Randomized, Double-Blind, Dose-Controlled Study to Assess the Efficacy and Safety of AQUAVAN® (Fospropofol Disodium) Injection for Minimal-to-Moderate Sedation in Patients Undergoing Colonoscopy
08/29/06	0160	Sent	Response to Request	Response to Request for information regarding Study 3000-0524
08/31/06	0161	Sent	Protocol Amendment	New Investigator-Protocol 3000-0522: Edward L. Cattau, M.D., Billy Wayne Long, M.D., Atul Shah, M.D., Muhammad Y. Sheikh, M.D., Protocol 300-0523: Neal D. Shore, M.D., FACS, Vadim David Vornik, M.D., Steven Winninger, M.D., CCTI, Protocol 300-0524: Khalid Almoosa, M.D., FCCP, Gregory J. Feldman, M.D. and

Date of Document	Sub. No.	Sent/ Rec'd	Type	Description
				Wilson Smith, Jr., M.D.
09/12/06	0162	Sent	Protocol Amendment	Change in Protocol 3000-0625: A Phase 1, Open Label, Single Dose, Cross-Over Pharmacokinetic/Pharmacodynamic Study of AQUAVAN® (fospropofol disodium) Injection Versus Diprivan® Injectable Emulsion in Volunteers
09/27/06	0163	Sent	Safety Report	15 Day Alert Report 2006MP001035
09/29/06	0164	Sent	Protocol Amendment	New Investigator-Protocol 3000-0523: Kyle Etzkorn, M.D., Richard Muckerman, M.D., Dasarathy Srinivas, M.D.., Protocol 3000-0524: Stephen Finberg, D.O., R. Kevin Jones, M.D., Keith J. Popovich, M.D., David Mathew Sellers, M.D., Austin Thompson III, M.D., Protocol 3000-0625: Thomas Hunt, M.D., PhD
10/03/06	0165	Sent	Information Amendment	Clinical Update-Airway Interventions-3nd Quarter, 2006
10/06/06	0166	Sent	Information Amendment	Statistical Analysis Plan (SAP) for Protocol 3000-0625: A Phase 1, Open Label, Single Dose, Cross-Over Pharmacokinetic/Pharmacodynamic Study of AQUAVAN® (fospropofol disodium) Injection Versus Diprivan® Injectable Emulsion in Volunteers
10/09/06	0167	Sent	Meeting Request	Request for Type B Pre-NDA Meeting
10/12/06	0168	Sent	Information Amendment	Clinical – 3000-0413-Statistical Analysis Plan: A Phase II, Randomized, Open-Label Study to Examine the Safety and Efficacy of AQUAVAN® Injection for Sedation of Patients Requiring Intubation and Mechanical Ventilation in the Intensive Care Unit Setting
10/18/06		Received	Telephone Contact	Contact from FDA regarding Pre-NDA Meeting
10/20/06		Received	Response to Meeting Request	FDA Meeting scheduled for Monday, January 29, 2007
10/31/06	0169	Sent	Protocol Amendment	New Investigator-Protocol 3000-0413: Richard Riker, M.D, Protocol 3000-0522: Jack R. Groover, M.D., F.A.C.P., Michael F. Kestell, M.D., and Bruce Schneider, M.D., Protocol 3000-0523: Paul Diehl, M.D., Robert Hardi, M.D.and Neal Shore, M.D., Protocol 3000-0524: Richard Barbers, M.D., Michael Chisdak, M.D., Gordon Downie, M.D., Ph.D., Boris Murillo, M.D., Jeffrey Rehm, M.D., Richard Sellman, M.D. and Barry William Sigal, M.D.
11/30/06	0170	Sent	Protocol Amendment	New Investigator-Protocol 3000-0523: Evan Ekman, M.D., Protocol 3000-0524: Robert Balk, M.D., Victor J. Cardenas, Jr. M.D., Arthur Gelb, M.D. and Carlos Orozco,

Date of Document	Sub. No.	Sent/ Rec'd	Type	Description
				M.D.
12/20/06	0171	Sent	Meeting Package	January 29, 2007 Pre-NDA Meeting Briefing Package, Volume 1 and Volume 2
01/02/07	0172	Sent	Protocol Amendment	New Investigator-Protocol 3000-0523: Maciej L. Dryjski, M.D. and Tong Joo Gan, M.D., Protocol 3000-0524: Momen Wahidi, M.D.
01/09/07		Sent	Phone Contact	Confirmation of receipt of Briefing Package and FDA to have responses to MGI's question by 1/26/07
01/26/07		Sent	Email	Updated list of attendees to the pre-NDA meeting on 01/29/07
01/26/07		Received	Email	FDA response to pre-NDA Meeting questions
01/31/07	0173	Sent	Protocol Amendment	New Investigator-Protocol 3000-0522: Jack R. Groover, MD, FACP, Douglas Rex, MD, Atul Shah, MD, Rodger Sleven, MD and Ira E. Stein, MD, Protocol 3000-0523: Kyle Etzkorn, MD, FACP, Robert Hardi, MD, Anthony Martin, MD and Vadim Vornik, MD, Protocol 3000-0524: Gerald O'Brien, MD
02/12/07		Received	Meeting Minutes	FDA Meeting Minutes from 1/29/07 meeting
02/28/07	0174	Sent	Protocol Amendment	New Investigator-Protocol 3000-0522: John Wber, M.D., Protocol 3000-0523: Ira. J. Gottlieb, D.P.M., Robert Hardi, M.D., Anthony E. Martin, M.D., Richard Muckerman, M.D. and Steven Wininger, M.D., C.C.T.I., Protocol 3000-0524: Gregory J. Feldman, M.D., Boris Murillo, M.D., Gerald O'Brien, M.D., Barry William Sigal, M.D., Gerard A. Silvestri, M.D. and Wilson Smith, Jr., M.D.
03/14/07		Sent	Letter	Baxter DMF 13246 authorization sent to FDA
03/14/07		Sent	Letter	Baxter DMF 10304 authorization sent to FDA
03/30/07	0175	Sent	Protocol Amendment	New Investigator-Protocol 3000-0522: Harry Wasvary, M.D., Protocol 3000-0523: Maciej L. Dryjski, M.D. and Richard Muckermann, M.D., Protocol 3000-0524: Gordon Downie, M.D., PhD., James R. Hansbrough, M.D., PhD. and R. Kevin Jones, M.D.
04/18/07	0176	Sent	Information Amendment	Statistical Analysis Plan (SAP) for Protocol 3000-0523 and 3000-0524
04/26/07	0177	Sent	Information Amendment	Transfer of Obligations for Protocol 3000-0523

Date of Document	Sub. No.	Sent/ Rec'd	Type	Description
05/16/07	0178	Sent	Information Amendment	Clinical-Airway Assistance Report
05/17/07	0179	Sent	Annual Report	Period March 29, 2006 – March 15, 2007
05/31/07	0180	Sent	Protocol Amendment	New Investigator-Protocol 3000-0523: Vinod K. Rustgi, M.D.
06/29/07	0181	Sent	Protocol Amendment	New Investigator-Protocol 3000-0413: Jeffrey Littman, M.D., Protocol 3000-0523: Vasanth K. Bethala, M.D., F.A.C.P, F.A.C.C , F.S.C.A, Evan R. Goldfischer, and M.D., Dasarathy Srinivas, M.D., Protocol 3000-0524: Richard Barbers, M.D., Victor J. Cardenas, Jr., M.D., Gregory J. Feldman, M.D., Keith J. Popovich, M.D. and Jeffrey Rehm, M.D.
07/24/07	0182	Sent	General Correspondence	Follow-Up Information from Pre-NDA Meeting of January 29, 2007
07/30/07	0183	Sent	Information Amendment	Transfer of Obligations for protocol 3000-0522 and revised transfer of obligations for protocol 3000-0524
07/31/07	0184	Sent	Protocol Amendment	New Investigator – Protocol 3000-0413: Kent Pearson, M.D., Protocol 3000-0524: Richard Barbers, M.D., Gregory J. Feldman, M.D., Stephen Finberg, D.O., James M. Fuller, M.D., Arthur Gelb, M.D., R. Kevin Jones, M.D., Carmel Joseph, M.D., Boris Murillo, M.D., David Phillips, M.D., Emory Robinette, M.D., Allan Seibert, M.D., Wilson Smith Jr., M.D and Momen Wahidi, M.D.
08/31/07	0187	Sent	Information Amendment	Toxicology Reports
08/31/07	0186	Sent	Protocol Amendment	New Investigator – Protocol 3000-0523: Robert Hardi, M.D. and Richard Muckerman, M.D.
08/31/07	0185	Sent	Information Amendment	Toxicology Reports: 03T-22169-01, 22737, 22738, and 22739
09/07/07	0188	Sent	Information Amendment	Toxicology Reports
09/17/07	0189	Sent	Information Amendment	Toxicology Report: 3000-15715-01-02G
09/28/07	0190	Sent	Protocol Amendment	New Investigator – Protocol 3000-0524: Richard Barbers, M.D., Michael Chisdak, M.D., Richard Kahn, M.D. and Gerald O'Brien, M.D.
11/30/07	0191	Sent	Protocol Amendment	New Investigator – Protocol 3000-0524: David Handshoe, M.D.

Date of Document	Sub. No.	Sent/ Rec'd	Type	Description
01/31/08	0192	Sent	Protocol Amendment	New Investigator – Protocol 3000-0524: Allan Seibert, M.D.
02/11/08	0193	Sent	Information Amendment	Transfer of Obligations for 3000-0522 and 3000-0524 to Almac Clinical Services
02/12/08	0194	Sent	Information Amendment	Transfer of Obligations to Almac Clinical Services for 3000-0524-diagram was left-out of submission No. 0193
07/01/08	0195	Sent	General Correspondence	Re: Sponsor Name Changes
07/07/08	0196	Sent	Annual Report	Annual Report

NDA CHRONOLOGY FOR LUSEDRA™

Sequence Number	Date of Document	Supplement Number	Sent/ Rec'd	Type	Description
	09/27/07		Sent	FDA Notification	Notification to Detroit FDA District Office of Electronic Filing of NDA 22-244
	09/27/07		Sent	FDA Notification	Notification to Baltimore FDA District Office of Electronic Filing of NDA 22-244
0000	09/27/07		Sent	Original NDA	Submission of electronic NDA in CTD format Electronic NDA in CTD format sent via FDA ESG – Receipt by CDER
	10/11/07		Received	Request for Information	FDA email request for electronic copy of carton/container labels in color and MGI 11/06/07 email response documents were submitted via the ESG
	10/15/07		Received	Acknowledgement	FDA Acknowledgement of receipt of AQUAVAN NDA 22-244
	10/30/07		Received	Request for Information	FDA request for PK concentration for pc.xpt and MGI 11/06/07 email response documents were submitted via the ESG
0001	11/05/07		Sent	Amendment – Response to request for Information	Labeling / PK dataset for 3000-0521
0001	11/06/07		Received	Acknowledgement	FDA CDER eReceipt of AQUAVAN 0001 via ESG
0002	11/07/07		Received	Acknowledgement	FDA CDER eReceipt of AQUAVAN 0002 via ESG
0002	11/07/07		Sent	Amendment – Response to request for Information	Highlights of Clinical Pharmacology
	11/07/07		Sent	Email	Confirmation that the Highlights of Clinical Pharmacology table was submitted, as requested on 10/30/07
	11/14/07		Received	Email Request	FDA request to provide verification studies of test methods and MGI's 11/16/07 response that the request was submitted through the esg

Sequence Number	Date of Document	Supplement Number	Sent/ Rec'd	Type	Description
	11/15/07		Received	Email Request	FDA request for street address of Cardinal Health and MGI's 11/16/07 response that the request was submitted through the esg
0003	11/16/07		Received	Acknowledgement	FDA CDER eReceipt of AQUAVAN 0003 via ESG
0003	11/16/07		Sent	Amendment – Response to request for Information	3.2.A.1 Facilities and Maintenance Report – Exhibit 19
	11/16/07		Received	Phone Contact	FDA request for information regarding the 5 clinical site inspections
	11/20/07		Sent	Email	FDA ESG – Submission to CDER Missing Files
	11/21/07		Sent	Email	Email explaining the path for sequences 0001 and 0003
	11/21/07		Sent	Response to Request for Information	Email w/zip file of Sequence 0001 - PK dataset for 3000-0521
	11/26/07		Received	Phone Contact	Advisory Committee could be as early as March 11th or as late as May 31st. FDA also indicated that AQUAVAN would be accepted for filing
0004	11/30/07		Received	Acknowledgement	FDA CDER eReceipt of AQUAVAN 0004 via ESG
0004	11/30/07		Sent	Amendment – Safety – Response to Request for Information	CRFs/IPLs/Protocols/1572s
	11/30/07		Sent	Email	Email to FDA with proposed revision to the indication statement
	11/30/07		Sent	Phone Contact	Phone contact to gain a better understanding of FDA's thinking for deciding that the NDA proposed two indications
	12/05/07		Sent	Response to Request	Response to FDA request for email of submission 0003

Sequence Number	Date of Document	Supplement Number	Sent/ Rec'd	Type	Description
	12/06/07		Received	Phone Contact	FDA confirmed receipt of materials for site inspections and for the remainder of the year a new contact if needed
	12/11/07		Sent	Phone Contact	Phone contact regarding the 74-day letter, which is awaiting signature
	12/13/07		Received	Email Response	FDA email response that the AQUAVAN application has been accepted for filing
	12/14/07		Received	Filing Communication	NDA application is sufficiently complete and fileable and potential review issues
	12/14/07		Sent	Email	Email to FDA as to the status of the 74-day letter
	12/18/07		Received	Email	FDA email looking at May 13-14th for Advisory Committee meeting
0005	01/03/08		Received	Acknowledgement	CDER eReceipt of Aquavan 0005 via ESG
0005	01/03/08		Sent	Response to Request	New protocol deviation listings for Study 3000-0522, Sites 303 and 518
	01/17/08		Received	Phone Contact	FDA phone contact requesting MGI to remove Accugenix from the NDA
0006	01/25/08		Received	Acknowledgement	CDER eReceipt of Aquavan 0006 via ESG
0006	01/25/08		Sent	Amendment – 4-Mos Safety Update	4-Month Safety Update
	01/30/08		Received	Email	FDA email noting the Advisory Committee meeting is changed to May 7, 2008
	01/31/08		Sent	Phone Contact	Request for MGI contact information
	01/31/08		Sent	Email	Questions to FDA and their response regarding Advisory Committee Meeting

Sequence Number	Date of Document	Supplement Number	Sent/ Rec'd	Type	Description
	01/31/08		Sent	Phone Contact	FDA request for original Clinical documents be made available for 2/5/08 inspection of studies 3000-0522 and 3000-0524
	02/01/08		Sent	Response to Request	Email response for contact information
	02/06/08		Received	Email Request	FDA comments and request for status of answering the 74-day requests
	02/11/08		Received	Email	FDA letter regarding preparations for the May 7, 2008 ALSDAC Committee Meeting
	02/11/08		Received	Email	Email of letter with requirements for the upcoming May 7, 2008 Advisory Meeting
	02/12/08		Sent	Email	Email to FDA with teleconference call-in information
	02/12/08		Received	Phone Contact	FDA response to MGI 2/8 and 2/12 voicemail and set up teleconference for 9:00 a.m., 2/15/08
	02/14/08		Sent	Email	Email to FDA seeking clarification regarding CYP interactions
0007	02/15/08		Received	Acknowledgement	CDER eReceipt of Aquavan 0007 via ESG
0007	02/15/08		Sent	Response to Request	Response to Filing Communication – Stability Summary and Data
	02/15/08		N/A	Meeting Minutes	MGI Meeting Minutes of 2/15/08 teleconference with FDA
	02/15/08		Received	Email	FDA email requesting non-clinical historical control data
	02/20/08		Sent	Email	Email to FDA to request names of 2/15/08 FDA teleconference attendees
0008	02/26/08		Received	Acknowledgement	CDER eReceipt of Aquavan 0008 via ESG

Sequence Number	Date of Document	Supplement Number	Sent/ Rec'd	Type	Description
0008	02/26/08		Sent	Response to Request	Response to Filing Communication - Manufacturers
0009	02/29/08		Received	Acknowledgement	CDER eReceipt of Aquavan 0009 via ESG
0009	02/29/08		Sent	Response to Request	Response to Filing Communication – Toxicology Reports
0010	03/06/08		Received	Acknowledgement	CDER eReceipt of Aquavan 0010 via ESG
0010	03/06/08		Sent	Response to Request	Response to Filing Communication – Non-Clinical Literature References
	03/20/08		Received	Email Request	FDA request regarding bacterial endotoxin qualification data and MGI's response that this information was submitted 11/15/907
0011	03/21/08		Received	Acknowledgement	CDER eReceipt of Aquavan 0011 via ESG
0011	03/21/08		Sent	Response to Request	Response to Request for tradename choices
	03/27/08		Received	Email	Email to and from FDA - Clarification that the upcoming ALSDAC meeting is not a joint meeting with Gastrointestinal Drugs
0012	3/28/08		Received	Acknowledgement	CDER eReceipt of Aquavan 0012 via ESG
0012	3/28/08		Sent	Response to Request	Response to Request – Stability Data
	04/03/08		Received	Email	FDA's request regarding bacterial endotoxin qualification data is no longer needed after checking the information submitted 11/15/907
0013	04/07/08		Received	Acknowledgement	CDER eReceipt of Aquavan 0013 via ESG
0013	04/07/08		Sent	Briefing Package	Briefing package for Advisory Committee Meeting

Sequence Number	Date of Document	Supplement Number	Sent/ Rec'd	Type	Description
	04/07/08		Sent	Briefing Package	Delivered 10 paper copies and 40 CD ROMs of Briefing Package to FDA
	04/07/08		Received	Email	Emails Regarding Delivery of Briefing Document
	04/07/08		Received	Email	Emails Regarding Delivery of Briefing Document and CDs
	04/11/08		Received	Phone Contact	FDA requested draft slides for the ALSDAC meeting for Dr. Rappaprt, as he will be unable to attend; Dr. Roca will head the meeting
	04/11/08		Received	Email	FDA Email requesting Names of Speakers and a PDF copy of the redacted Briefing Materials
	04/11/08		Sent	Phone Contact	Phone contact regarding the Advisory Committee Meeting and FDA request for MGI's list of attendees
0014	04/15/08		Received	Acknowledgement	CDER eReceipt of Aquavan 0014 via ESG
0014	04/15/08		Sent	Response to Request	Response to Request for Slides for Advisory Committee Meeting
	04/15/08		Sent	Email	Emailed the names of speakers and external consultants attending the advisory meeting
	04/15/08		Sent	Email	Emailed the draft meeting slides to FDA
	04/16/08		Sent	Email	Email request for telecom regarding abuse liability
	04/17/08		Received	Email	FDA Background Package and memo sent to the committee members (See phone contact for cover letter)
	04/17/08		Received	Phone Contact	FDA voicemail stating background package was being sent via FEDEX and the cover letter faxed
	04/18/08		Received	Email	FDA moved telecom to 04/25 so MGI can review some preliminary comments

Sequence Number	Date of Document	Supplement Number	Sent/ Rec'd	Type	Description
	04/18/08		Sent	Email	Email regarding moving the telecom to 4/25/08 regarding abuse liability
	04/20/08		Received	Phone Contact	FDA decided to schedule one teleconference in place of two for April 24, 11:00 am to 1:00 pm
	04/21/08		Sent	Email	Email to FDA with update request of status of the micro information.
	04/22/08		Received	Letter	FDA Discipline Review Letter regarding abuse liability by the Controlled Substance staff
	04/23/08		Received	Email	FDA Request and MGI's response for list of investigators
	04/24/08		Sent	Phone Contact	Phone contact regarding meeting specifics
	04/24/08		Received	Email	FDA Request for dosing information to be presented at today's teleconference
	05/01/08		Received	Email	FDA response to meeting room set-up
	05/01/08		Sent	Email	Email sent to FDA with the proposed room set-up for the Committee meeting
	05/01/08		Sent	Phone Contact	Phone contact to discuss MGI response to ASA letter to the committee and meeting information and set-up
	05/01/08		Sent	Letter	Letter and poster presentations sent to FDA for a better understanding of the clinical pharmacology of phospropofol (hard copy and CD) (to be formally submitted at a later date)
	05/01/08		Sent	Email	Draft labeling text emailed to FDA (to be formally submitted)
	05/07/08		Received	FDA Correspondence	FDA draft Agenda for May 7, 2008 Meeting

Sequence Number	Date of Document	Supplement Number	Sent/ Rec'd	Type	Description
	05/07/08		Received	FDA Correspondence	FDA Background Package for May 7, 2008 Meeting
	05/13/08		Received	Letter	Italy's request for further documentation to process DMF request
0015	05/15/08		Received	Acknowledgement	CDER eReceipt of Aquavan 0015 via ESG
0015	05/15/08		Sent	Compilation of Advisory Committee Meeting Material	ASA Letter, Sponsor Presentation, and Investigator List
	05/19/08		Received	Email	Emails regarding the micro information request
	05/20/08		Received	Email	FDA request for clarification on pediatric plan
0016	05/21/08		Received	Acknowledgement	CDER eReceipt of Aquavan 0016 via ESG
0016	05/21/08		Sent	Response to Request	Efficacy information amendment
0017	05/23/08		Received	Acknowledgement	CDER eReceipt of Aquavan 0017 via ESG
0017	05/23/08		Sent	Response to Request	Request Deferral Pediatric Studies - Information amendment
	05/23/08		Sent	Email	Email to FDA that pediatric plan was submitted through the gateway
	05/27/08		Received	Email	FDA email regarding availability for telecom with micro reviewer
	05/28/08		Received	Email	Emails regarding CMC information request
	05/28/08		Received	Email	Emails regarding CMC information request

Sequence Number	Date of Document	Supplement Number	Sent/ Rec'd	Type	Description
	05/28/08		Sent	Phone Contact	Left a voicemail message noting receipt of email regarding Fluoro Tec stoppers, starting time for meeting, and status of MGI's 8 factor analysis regarding controlled substance scheduling
	05/28/08		Received	Email	Emails Regarding CMC Request - Stopper Material
	05/28/08		Received	Phone Contact	Phone contact to discuss if validation batches were complete and if hold time information was available
	05/29/08		Received	Email	Emails regarding a complete and comprehensive risk management submission
	05/29/08		Received	Email	FDA email discussing a comprehensive risk management plan
0018	05/30/08		Received	Acknowledgement	CDER eReceipt of Aquavan 0018 via ESG
0018	05/30/08		Sent	Response to Request	Efficacy Information Amendment with Child-Pugh Scores
	06/04/08		Received	Email	Emails regarding the PK parameters information request
0021	06/06/08		Received	Acknowledgement	CDER eReceipt of Aquavan 0021 via ESG
0021	06/06/08		Sent	Response to Request	Quality Information Amendment UV Scan, Module 3 Drug Sub Spec-Stability, Drug Product Post-Approval Stability
0020	06/06/08		Received	Acknowledgement	CDER eReceipt of Aquavan 0020 via ESG
0020	06/06/08		Sent	Response to Request	Quality Information Amendment for Product Hold Times
0019	06/06/08		Received	Acknowledgement	CDER eReceipt for Aquavan 0019 via ESG
0019	06/06/08		Sent	Response to Request	Efficacy Information Amendment for Patients with Hepatic Impairment

Sequence Number	Date of Document	Supplement Number	Sent/ Rec'd	Type	Description
0022	06/09/08		Received	Acknowledgement	CDER eReceipt of Aquavan 0022 via ESG
0022	06/09/08		Sent	Response to Request	Abuse Liability Assessment
	06/10/08		Received	Email	Emails regarding submission of the 8 factor analysis
0023	06/13/08		Received	Acknowledgement	CDER eReceipt of Aquavan 0023 via ESG
0023	06/13/08		Sent	Response to Request	Risk Evaluation and Management Plan
	06/17/08		Received	Email	Emails regarding 6/19/08 scheduled labeling teleconference
	06/25/08		Received	Email	Email with Label for Eisai Review
	06/25/08		Received	Email	FDA email with AQUAVAN label
	06/26/08		Received	Email	FDA email regarding labeling comment
	06/26/08		Sent	Phone Contact	Phone contact to discuss AQUAVAN label and tradename
	06/26/08		Sent	Email	Emails discussing contact person for next week
	06/27/08		Sent	Email	Email to FDA with Proposed Aquavan Label
	06/27/08		Sent	Email	Email with Dial-in Information
	06/27/08		Sent	Email	Email with attached proposed draft labeling to FDA Project Manager

Sequence Number	Date of Document	Supplement Number	Sent/ Rec'd	Type	Description
0024	06/27/08		Received	Acknowledgement	CDER eReceipt of Aquavan 0024 via ESG
0024	06/27/08		Sent	Response to FDA's proposed labeling changes	Draft Labeling Submission
	06/30/08		N/A	Telephone Conference	Aquavan® NDA 22-244
	07/02/08		Sent/ Received	General Correspondence	Re: Sponsor Name Change
0025	07/02/08		Sent/ Received	Compliance Notification	Re: Sponsor Name Change
0026	07/03/08		Sent	Response to FDA Request	Re: Response to Request from FDA
	07/08/08		N/A	Telephone Conference	Fospropofol Disodium Label
	07/08/08		Sent/ Received	E-Mail	Aquavan® NDA 22-244
	07/11/08		Sent/ Received	E-Mail	No further outstanding requests for information from FDA
	07/11/08		Sent/ Received	E-Mail	No further outstanding requests for information from FDA
	07/11/08		Sent/ Received	E-Mail	FDA Participants for July 8, 2008 Telephone Conference
	07/11/08		Sent/ Received	E-Mail	Eisai Participants for July 8, 2008 Telephone Conference
0027	07/11/08		Sent	Response to FDA Request	Re: Response to FDA Request

Sequence Number	Date of Document	Supplement Number	Sent/ Rec'd	Type	Description
	07/21/08		Sent/ Received	E-Mail	Fospropofol PDUFA Date Email with FDA
	07/23/08		Recieved	Incoming FDA Correspondence	Aquavan® NDA 22-244 July 7, 2008 Not Approvable Action Letter
	07/23/08		Received	FDA Correspondence	FDA Not Approvable Letter
0028	08/04/08		Sent	Response to FDA Request	Re: Response to Action Letter
0029	08/07/08		Sent	Request for Meeting	Re: Request for Type A Meeting
	08/08/08		Sent/ Received	E-Mail	Meeting Request E-mail
	08/25/08		Received	Incoming FDA Correspondence	Type A Meeting - Aquavan® NDA 22-244
	09/02/08		N/A	Telephone Conference	Aquavan® NDA 22-244 - DDMAC Process Question
	09/11/08		Sent/ Received	E-Mail	Aquavan® NDA 22-244 Responses from Meeting Package dated August 7, 2008
	09/11/08		Sent/ Received	E-Mail	Aquavan® NDA 22-244 Meeting Request email to FDA dated August 8, 2008
	09/11/08		Sent/ Received	E-Mail	Aquavan® NDA 22-244 Email correspondence with FDA
	09/11/08		Sent/ Received	E-Mail	Aquavan® NDA 22-244 Action Letter Question to FDA dated August 8, 2008
0030	09/12/08		Sent	General Correspondence	Re: Type A Post-Action Meeting Minutes

Sequence Number	Date of Document	Supplement Number	Sent/ Rec'd	Type	Description
	10/07/08		Sent/ Received	E-Mail	Fospropofol Package Insert
	10/08/08		Sent/ Received	E-Mail	Fospropofol Package Insert - FDA's meeting minutes
0031	10/13/08		Sent	Resubmission	Re: Complete Amendment to Not Approvable Letter
0032	10/23/08		Sent	Labeling Supplement	Re: Resubmission of SPL Due to Filename Error
	10/24/08		Sent/ Received	E-Mail	Sequence 0033 email sent by Eisai to FDA of Proposed Pediatric Plan
0033	10/24/08		Sent	General Correspondence	Re: Proposed Plan for Pediatric Studies
	11/04/08		Received	Incoming FDA Correspondence	LUSEDRA™ NDA 22-244 Acknowledgement of Complete Response
	11/12/08		Sent/ Received	E-Mail	LUSEDRA™ NDA 22-244 AIFA Authorization for Manufacture of Fospropofol at Archimica, Italy
	12/01/08		Sent/ Received	E-Mail	LUSEDRA™ NDA 22-244 FDA Draft Label 11-18-2008
	12/01/08		Sent/ Received	E-Mail	LUSEDRA™ NDA 22-244 Eisai Proposed Label 11-21-2008
	12/02/08		Received	Incoming FDA Correspondence	LUSEDRA™ NDA 22-244 Carton/Conatiner Labels
	12/05/08		Sent/ Received	E-Mail	LUSEDRA™ NDA 22-244 Proposed Pediatric Dates 12-5-08
	12/05/08		Sent/ Received	E-Mail	LUSEDRA™ NDA 22-244 Labeling Negotiations

Sequence Number	Date of Document	Supplement Number	Sent/ Rec'd	Type	Description
	12/05/08		Sent/ Received	E-Mail	LUSEDRA™ NDA 22-244 Carton and Container Labels 12-04-08
	12/09/08		Sent/ Received	E-Mail	LUSEDRA™ NDA 22-244 FDA Revised Label 12-04-08
	12/09/08		N/A	Telephone Conference	LUSEDRA™ NDA 22-244 FDA Meeting Synopsis 12-04-08
	12/09/08		Sent/ Received	E-Mail	LUSEDRA™ NDA 22-244 Emails Re PI and Carton/Container Labels 12/2-9/08
	12/09/08		Sent/ Received	E-Mail	LUSEDRA™ NDA 22-244 Carton/Container Labels Revised per FDA Request 12-09-08
0034	12/09/08		Sent	Final Printed Labeling	Re:Final LUSEDRA™ Carton and Container Lables
	12/11/08		Sent/ Received	E-Mail	LUSEDRA™ NDA 22-244 Email Carton/Container Labels 12-11-08
	12/11/08		Sent/ Received	E-Mail	LUSEDRA™ NDA 22-244 Email Carton/Container Labels 12-11-08
0035	12/11/08		Sent	Final Printed Labeling	Re: LUSEDRA™ (fospropofol disodium) Injection Response to Request for Information
	12/12/08		Sent/ Received	FDA Correspondence	LUSEDRA™ NDA 22-244 Approval
	12/12/08		Sent/ Received	E-Mail	LUSEDRA™ NDA 22-244 Summary of Fospropofol FDA Communications 12-11-08
	12/12/08		Sent/ Received	E-Mail	LUSEDRA™ NDA 22-244 Summary of Fospropofol FDA Communications 12-11-08
0036	12/12/08		Sent	Product Correspondence	Re: Draft LUSEDRA Label (12-08-08)

Sequence Number	Date of Document	Supplement Number	Sent/ Rec'd	Type	Description
	12/16/08	0002	Sent	DDMAC	DDMAC POST MARKETING
0037	12/22/08		Sent	Final Printed Labeling	Re: LUSEDRA Final Structured Product Labeling